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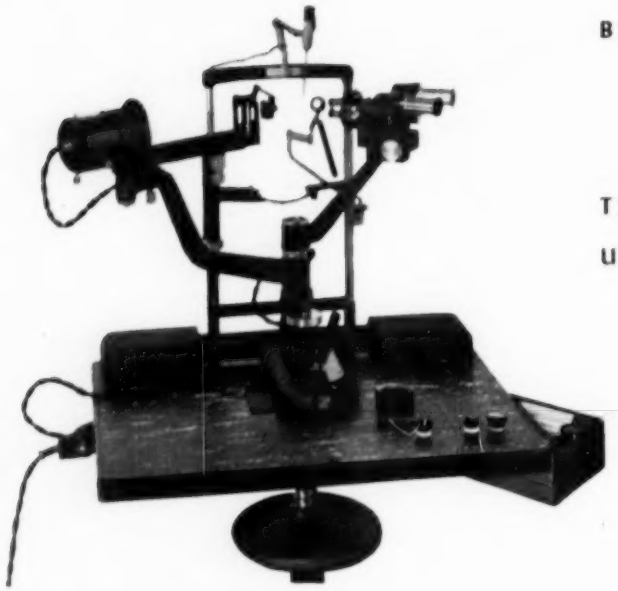

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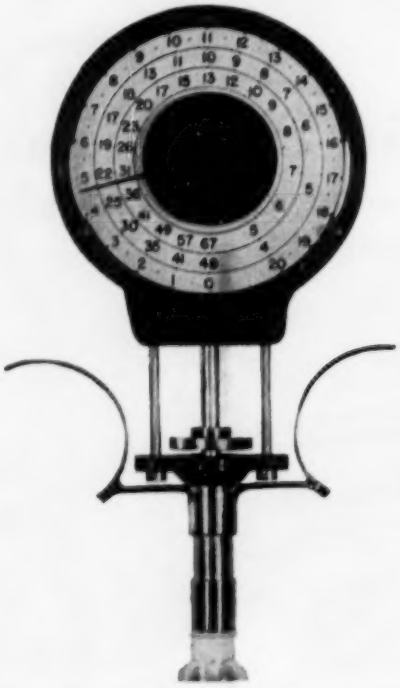

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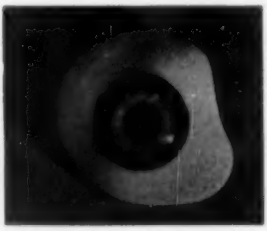

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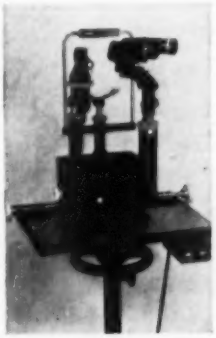

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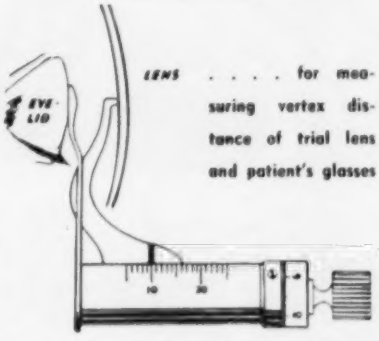

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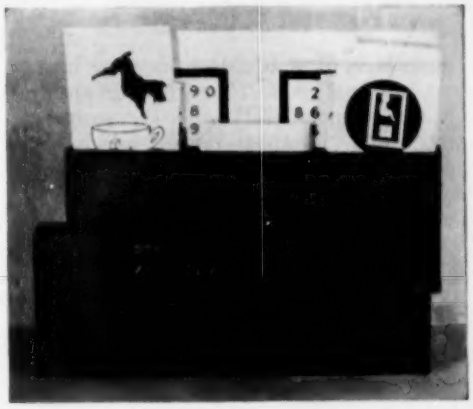

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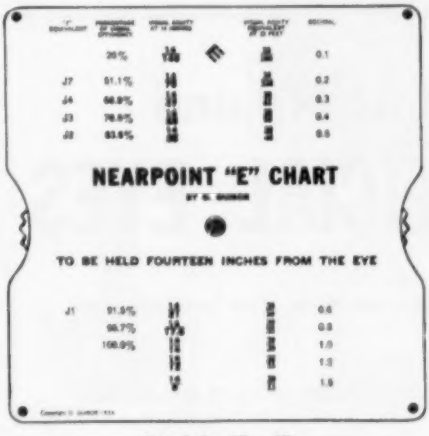

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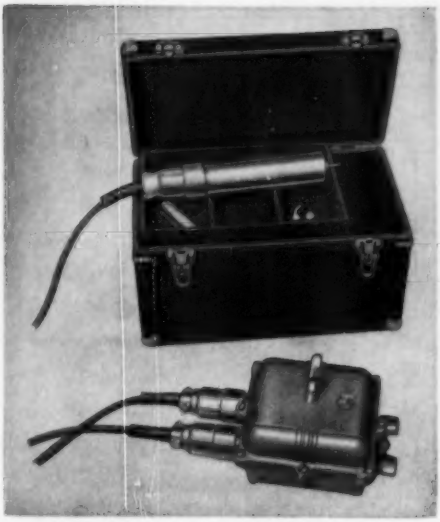

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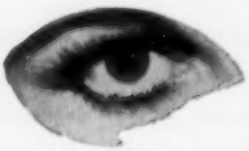

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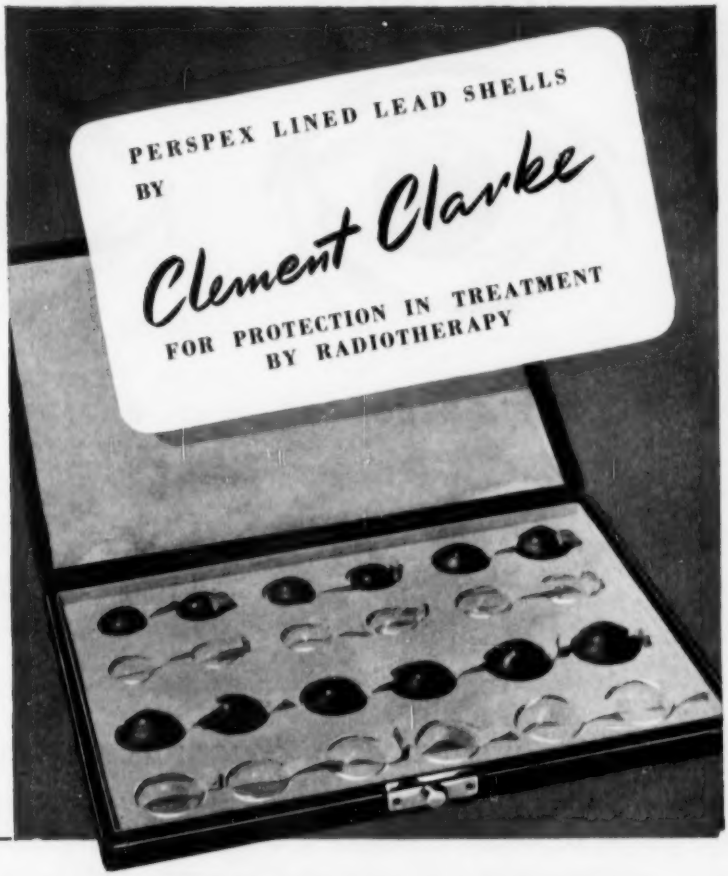

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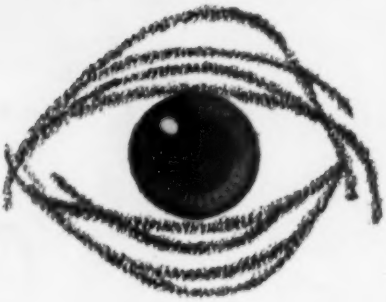

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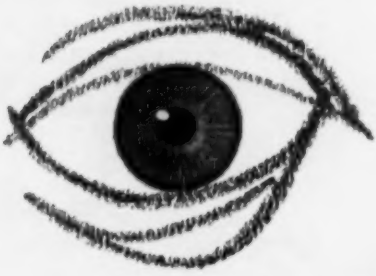

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1. Gettes, B. C., and Leopold, I. H.: A. M. A. Arch. of Ophth. 49:24 (Jan.) 1953.
2. Stolzar, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.

Editorials

LETTER FROM THE EDITORS

WE HOPE that you will like the "new look" of the ARCHIVES. The cover has been completely redesigned, and illustrations and space have been rearranged to present a maximum amount of material in the minimum compass compatible with good readability. The editors were somewhat disturbed by the fact that this is the second change in the format of the ARCHIVES in the last two years. However, they were glad to accede to the new proposal for the cover, provided it contained at least a partial list of the table of contents. The Board has consistently requested the Table of Contents on either the front or the back cover. Since this is also the most lucrative advertising space, the business management has just as consistently requested it for this purpose. The suggestion of having a partial list of the contents on the front cover has been accepted by the management, and the Board feels that this is a happy compromise.

It has been felt, in line with the policy of the Editorial Board to attempt to keep abreast of the major interest of all ophthalmologists by such innovations as the Annual Reviews, Scientific Exhibits, editorials on timely topics, etc., that some change in the physical form of the ARCHIVES was in order. The Board feels that the changes made are well conceived and executed. The editors will strive to do their part in selecting new, reliable, and informative material for the readers and in presenting it as promptly as possible.

THE EDITORIAL BOARD

NEUROFIBROMATOSIS AND CONGENITAL UNILATERAL PULSATING AND NONPULSATING EXOPHTHALMOS

ANDRÉ J. BRUWER, M.D.
AND
ROBERT R. KIERLAND, M.D.
ROCHESTER, MINN.

TWELVE years ago, at the 93rd Annual Session of the American Medical Association, the subject of pulsating exophthalmos was reviewed.[1] That survey encompassed 812 cases. In practically all those cases an arteriovenous shunt was apparently the basic factor responsible for the condition. It would seem that the term "pulsating exophthalmos" automatically implied the association of an arteriovenous communication in or immediately behind the orbit.

No mention was made at that time of a small group of cases of congenital unilateral pulsating exophthalmos in which there is no associated arteriovenous shunt and in which the roentgenologic findings are indicative of defective development of the sphenoid wings and of the orbital plate of the frontal bone. A number of such cases had been placed on the record by 1954, and some authors had found a curious relationship to neurofibromatosis, thus adding further to the mystery of that disease. Also, cases of congenital unilateral nonpulsating exophthalmos with similar roentgenologic findings have been described in association with neurofibromatosis. On the other hand, identical cases, but without the dermatologic findings of neurofibromatosis, have also been described.

The present paper deals with some aspects of this small group of cases of congenital, pulsating or nonpulsating, unilateral exophthalmos associated with neurofibromatosis. Similar cases have also been described in articles dealing with posterior orbital encephalocele[2] and in articles dealing with bone changes in neurofibromatosis.[3] "The condition is so characteristic that a mistake in diagnosis is unlikely, once the condition is known."[4]

One of the first descriptions of a case was given by Rockliffe[5] in 1900, and a follow-up report was given by Rockliffe and Parsons[6] in 1904. In 1899 a 22-month-old child had been brought to them because of pulsating exophthalmos of the right eye. The lids of the eye were somewhat thickened, and deep in the orbit a soft, cystic growth could be felt. No bruit was heard. At that time no conclusion was reached regarding the cause of the condition. Two years later the proptosis was so severe that the cornea was on a level with the alae of the nose and corneal ulceration had developed. In 1903 the eye was removed together with a large retro-orbital plexiform neuroma. The child died at operation. Necropsy revealed that the roof of the right orbit was absent. The lesser and greater wings of the sphenoid and the lacrimal plate of the ethmoid were also missing. The right cerebral hemisphere was considerably larger than the left. The pituitary body, optic chiasm, and adjoining soft and bony parts were displaced toward the left side.

Read before the Section on Radiology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 25, 1954.

From the Section of Roentgenology (Dr. Bruwer) and the Section of Dermatology (Dr. Kierland), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

It is noted from the cases in the literature that the condition usually attracts attention in the first few months or years of life. The features which are noted by the mother usually are the unilateral proptosis and a thickening of the upper lid. This thickening not infrequently extends into the temporal region of the involved side. In more advanced stages, the proptosis may be severe, the globe being extruded on the cheek, and there may be tremendous overgrowth and distortion of the tissues of the lids. Other stigmata of neurofibromatosis, such as hypertrophy of one side of the face or of a limb, skin nodules, and café au lait spots, may be present. However, in a number of cases,[7] and especially in those described as cases of posterior orbital encephalocele, the usual stigmata of neurofibromatosis have not been present. It is of interest to speculate whether these are cases of a forme fruste of neurofibromatosis, and it may be suggested that the relationship of posterior orbital encephalocele to neurofibromatosis may be similar (though in an equally obscure way) to the apparently close relation between intrathoracic meningocele and neurofibromatosis.*

It has been stated before that in most cases pulsating exophthalmos is secondary to an arteriovenous shunt, and in such cases auscultation in the region of the orbit discloses a bruit. In the type of case under discussion such a bruit is not heard.

Robertson [4] demonstrated in his case that the pulsation in the proptosed left eye decreased on compression of the left common carotid artery and was abolished when both common carotid arteries were compressed.

Gala [2] drew attention to the fact that the pulsation decreased proportionately to the amount of cerebrospinal fluid withdrawn by lumbar puncture.

Peyton and Simmons [9] reviewed the literature and found 20 cases of neurofibromatosis associated with a defect in the wall of the orbit. They concluded that the exophthalmos in these cases was due either to a retro-orbital tumor (neurofibroma or optic nerve glioma) or to encroachment on the orbit by the intracranial contents or to both factors. In those cases in which pulsation has been present, it has been demonstrated that the pulsation is transmitted directly from the brain and its surrounding cerebrospinal fluid to the orbital contents, and that the pulsation is synchronous with the radial pulse.* Wheeler [11] has, incidentally, shown that in cases of Hand-Schüller-Christian disease, in spite of a roentgenologic appearance of absence of the orbital roof, pulsation of the eye is not present. This is due to the buffering action of a thick layer of xanthomatous tissue.

ROENTGENOLOGIC APPEARANCE

The first adequate roentgenologic description is usually attributed to LeWald.[12] The four cases discussed by him were evaluated again by Wheeler, who added a similar case (but without pulsation) and discussed the mechanism of the pulsation. Various authors have described various degrees of involvement of the skull as seen on the roentgenogram, but the features usually seen are as follows.

Posteroanterior View.—The orbit on the involved side is generally larger in diameter than the opposite one. The inferior margin may lie much lower than it would normally and may show asymmetric deformity. The orbit has a "blank" appearance, owing to the fact that none of the usual landmarks are present. Thus, the temporal line is absent and the sphenoid ridge markedly elevated. The anterior clinoid process may be absent. The anterior ethmoid cells and the maxillary antrum

* References 10 and 11.

on the involved side may be small. The crista galli may be displaced toward the normal side. The floor of the middle cranial fossa may be deeper than that on the opposite side.

Lateral View.—A variable portion of the orbital plate of the frontal bone may be absent. The lesser wing of the sphenoid, the anterior clinoid process, and even the posterior clinoid process, may be absent or deformed. The sella is deformed and is scooped out on the involved side. The floor of the middle cranial fossa may be deepened, and the middle fossa usually extends farther forward than normally.

Optic-Canal View.—Five of the seven cases of neurofibromatosis of the orbit in Pfeiffer's [18] series presented striking enlargement of the optic canal, "suggesting involvement of the optic nerve or its sheath with neurofibroma. Since the field of

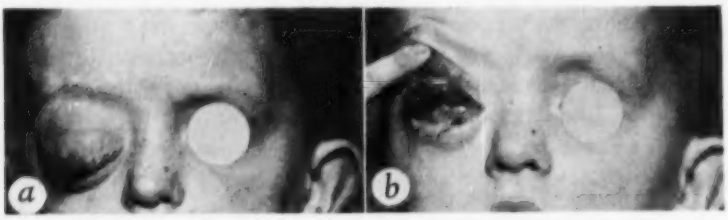

Fig. 1.—Pulsating exophthalmos and neurofibromatosis of the right upper lid.

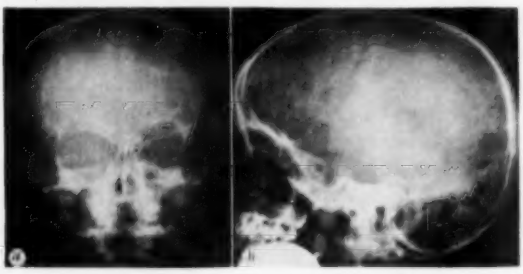

Fig. 2.—Enlarged right orbit, elevated sphenoid ridge, absent right anterior clinoid process, absent temporal line, deformed sella, and enlarged middle cranial fossa.

vision of three of these patients was normal, it did not seem likely that glioma of the optic nerve was present."

Base-of-Skull View.—This view is excellent for demonstration of anterior displacement of the middle fossa on the affected side. Deformities of the foramen ovale and foramen spinosum have also been demonstrated.

Body-Section Roentgenography.—This technique may be used for clearer demonstration of any of the abnormal features.

Encephalography.—This was performed in Robertson's case. The lateral ventricles were slightly enlarged, the anterior horn on the uninvolved side being larger than on the side with the proptosis. But the tip of the temporal horn on the involved side was larger than on the opposite side. A collection of gas was also seen in the involved orbit, extending to the posterior surface of the eyeball and suggesting the

presence of orbital encephalocele. It should be mentioned that dermatologic findings of neurofibromatosis were absent in Robertson's case, but that all other findings were identical to those in cases with dermatologic manifestations.

REPORT OF CASES

CASE 1.—A 4-year-old boy (Fig. 1), who was brought to the Mayo Clinic in June, 1945, had had since birth a downward displacement of the right eye, which had been associated with an enlarged, boggy right upper eyelid. The eyeball could be pushed into the socket readily. Just lateral to the right eye, and on the upper portion of the cheek, was a soft-tissue swelling. Another soft swelling involved the scalp in the left occipital region. There were many café au lait areas on the skin.

Roentgenograms of the skull at this time (Fig. 2) revealed that the right orbit was larger than the left. The posterior limit of the anterior cranial fossa (normally indicated by the sphenoid ridge) was markedly elevated in the posteroanterior view, owing to absence of the lesser wing of the sphenoid and absence of the posterior portion of the roof of the orbit. The right anterior clinoid process was absent, as was the temporal line. On the lateral view the pituitary fossa was

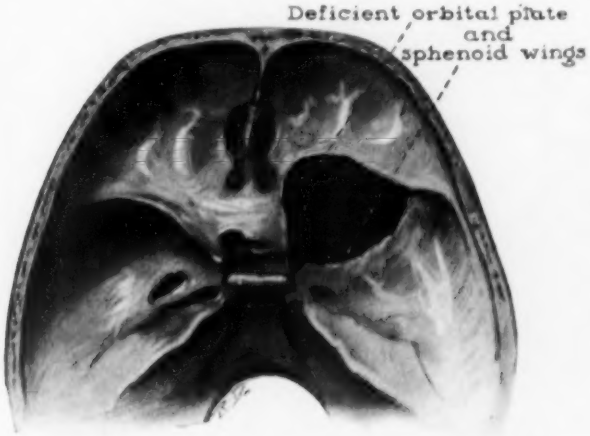

Fig. 3.—Diagrammatic representation of deficient development of the lesser and greater wings of the sphenoid and of the orbital roof, allowing the cerebral contents to herniate into the orbit.

enlarged and deformed, and the right middle fossa was enlarged in depth and length. The Towne view showed that the occipital bone was thinned, the deformity being of irregular outline and involving both sides.

A week later, transfrontal craniotomy was performed. The surgeon stated that the dura was densely adherent all along the coronal suture, giving the impression that this suture had closed in on a fold of dura. The sphenoid wing was markedly "eroded" and elevated, and the roof of the orbit was displaced upward but was of about normal thickness; that is, there was no distinct evidence of thinning, such as one would expect with an intraorbital tumor producing an orbit of this size. The sella was deformed, and this appeared to be due to the brain pressing down on it. In the superior orbital fissure the temporal lobe was densely adherent and projected into the orbit. It appeared as though it was the tip of the temporal lobe which had caused erosion or failure of development of the superior orbital fissure. Both optic nerves and the chiasm appeared normal. As a tumor was not found to account for the exophthalmos, the operation was terminated.

Two weeks later the mass in the left occipital region was partly removed. It was very adherent to the scalp, and caused a depression in the skull. The pathologist reported that it was a cystic neurofibroma. It appeared to originate on the greater occipital nerve.

Examination of the patient six months later revealed pulsation of the left eye. Some tissue removed at this time from the elephantiac right upper lid proved to be neurofibromatous.

In 1951 it was reported that convulsions had developed. Examination in 1953 disclosed that the proptosis was marked. The child was to return for evaluation regarding closure of the defect in the orbit, so that the temporal lobe might be kept from projecting into it.

In this case we have the combination of pulsating exophthalmos, café au lait areas, and roentgenographic findings of deficiency of the orbital landmarks. Operation showed that the temporal lobe was encroaching upon the orbital contents, this being the mechanism of the pulsating exophthalmos (Figs. 3 and 4). The deformity of the occipital region, associated with overlying neurofibroma, is the type of associated lesion previously described by Rosendal.[14]

Case 2.—A 3-year-old girl (Fig. 5) was referred to the Mayo Clinic with a diagnosis of arteriovenous aneurysm causing protrusion of the left eyeball. The mother had noted this pro-

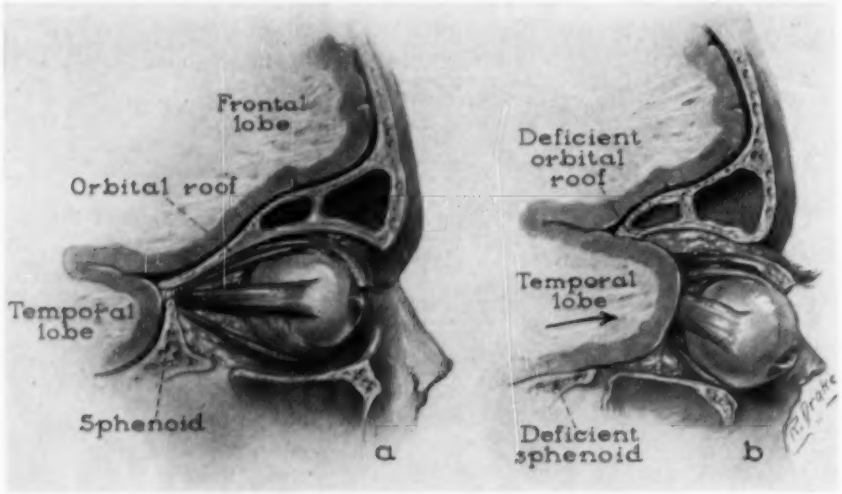

Fig. 4.—(*a*) Sagittal section through the normal orbit and middle cranial fossa. (*b*) Sagittal section showing encroachment of the cerebral contents on the orbital cavity in cases of proptosis and pulsating exophthalmos seen in neurofibromatosis.

trusion since birth. Since the first year the left side of the face had seemed somewhat larger than the right. For the same period there had been cramping of the muscles of the left calf, four or five times a day, unrelated to exercise. Since the age of 2 months café au lait areas had been developing, and these were becoming more numerous. When the child started to walk, she dragged the left leg a bit but had been steadily improving with regard to this difficulty.

Physical examination revealed no bruit. Vision was judged as bilaterally normal, and movements of the eyes were unimpaired.

Roentgenograms of the skull (Fig. 6) showed that the left orbit was larger than the right and that there were slight elevation of the sphenoid ridge and sligh lateral displacement of the temporal line. The sella was deformed, and the left anterior clinoid process was elevated and deformed. The foramen rotundum on the left was not seen.

Exploratory operation was refused.

The association of unilateral congenital proptosis and café au lait areas is again seen. The roentgenographic findings are somewhat less marked than usual, but they are very definite, especially the changes in the region of the sella.

CASE 3.—A 4-year-old girl (Fig. 7) was brought to the Mayo Clinic because of a swelling of the right upper lid. At the age of 3 months a small swelling had been noted at the outer canthus of the right eye. The swelling had gradually enlarged. At the age of 3 years it had been treated with roentgen rays, but without benefit.

Examination revealed a lumpy swelling of the right upper lid and fullness of the upper and lateral margin of the orbit, which, at ophthalmologic consultation, was thought to be due to a neurofibroma. On the trunk there were a number of café au lait areas and some soft balloon-like papules. The dermatologic diagnosis was neurofibromatosis.

Roentgenographic examination of the skull (Fig. 8) revealed marked forward enlargement of the right middle fossa, and the bony roof of the right orbit was very short. This resulted in upward displacement of the line forming the sphenoid ridge. The right orbit was considerably larger than the left.

Although the roentgenologic appearance of the orbit in Case 1 was very similar to that in Case 3, pulsating exophthalmos was present in Case 1 but not in Case 3.

Figure 5.—Case 2. See text for details.

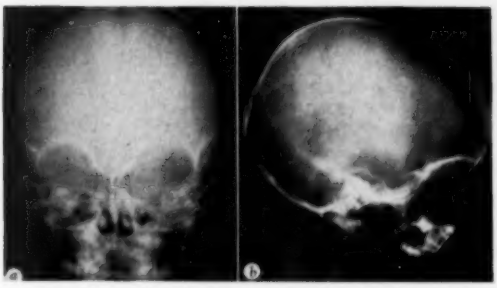

Fig. 6.—Left orbit enlarged, sphenoid ridge elevated, temporal line displaced laterally, left anterior clinoid process elevated, sella deformed, and left middle fossa slightly enlarged.

It is possible that, in spite of the roentgenographic similarity, the actual bony deficiency was smalled in Case 3. Wheeler suggested that it is probably necessary to have a considerable defect in the roof of the orbit for pulsation to occur.

CASE 4.—A 17-year-old youth (Fig. 9) was referred to the Mayo Clinic because of the findings by the referring physician, to be described. He had had an edematous, drooping right upper lid since birth. A slight pulsating exophthalmos had been found, but no bruit was detected. Multiple café au lait areas were present on the trunk and extremities. Roentgenograms of the skull disclosed bulging of the middle cranial fossa on the right, and it was noted that this was similar to that seen in some cases of subdural hygroma. The encephalogram had demonstrated that the right temporal horn protruded far forward.

Examination at the Clinic confirmed the previous findings. Field examination of the eyes gave essentially negative results. One observer stated that pulsation of the right eye disappeared on compression of the right common carotid artery. A family history, on the father's side, of anomalies associated with neurofibromatosis was elicited. The patient's main concern was with the appearance of the right upper eyelid.

Examination of the roentgenograms of the head (Fig. 10) revealed that the right orbit was larger than the left. The temporal line was absent, and the posterior margin of the floor of the anterior cranial fossa was displaced far forward. The middle fossa was greatly enlarged forward, and the anterior clinoid process on the right was not seen. The anterior ethmoid cells on the right were smaller than those on the left and were opaque.

Right transfrontal craniotomy was performed. About 3 mm. lateral to the right optic canal there was a huge defect in the orbit, and the tip of the temporal lobe extended into the orbit. The tip of the temporal lobe was covered by greatly thickened pia-arachnoid. No evidence of neoplasm was found. A piece of Ivalon surgical sponge was used to close the defect in the posterior orbital wall.

Although there was some postoperative fever and puffing of the eye, a letter from the mother a few weeks later stated that there had been considerable improvement.

Fig. 7.—Neurofibromatosis of right upper eyelid.

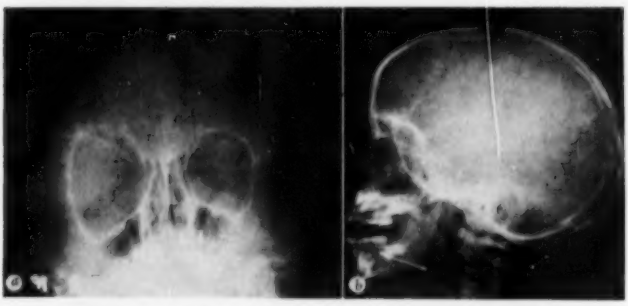

Fig. 8.—Enlarged right orbit, elevated sphenoid ridge, absent temporal line, markedly enlarged right middle fossa, and deformed sella.

The obvious cause of the pulsating exophthalmos—protrusion of the temporal lobe into the orbit—was again demonstrated in this case. The finding of thickened pia-arachnoid over the temporal lobe is similar to that in Avizonis'† case.

Case 5.—An 11-month-old boy was brought to the Mayo Clinic because of a swelling of the left temple, of one month's duration. An asymptomatic swelling of the left upper lid was noted at about the age of one month, and a physician had diagnosed it as an excess of lacrimal tissue.

Examination revealed a left supraorbital swelling, as well as a swelling of the left temporal region. On palpation of the latter swelling, there was a feeling as of the edges of separated bone sutures. The left eye was displaced downward and inward. An examining physician noted discrete, colorless papules in the supraclavicular regions. The ophthalmologist mentioned the possibilities of lymphangioma, meningocele, and neurofibromatosis. The child was taken home, but returned seven months later for further evaluation of his condition. At this time the findings were as before, but a definite pulsation of the globe was noted. There was no bruit.

† Avizonis, P., cited by Rosendal,[14] pp. 385, 386, and 388.

Roentgenograms of the skull (Fig. 11) disclosed that the swelling in the left temporal region was due to a crater-shaped opening of the sphenoid fontanelle. The left orbit was larger than the right; the left sphenoid ridge was greatly elevated, and the temporal line was absent. The anterior clinoid process on the left appeared elevated.

Left frontotemporal craniotomy was performed. A congenital anomaly of the sphenoid was found but not described. An extensive neurofibroma of the left orbit was present, and it also involved the dura over the tip of the temporal lobe. Subtotal removal of the tumor and involved dura was done and the defect covered with animal membrane.

Fig. 9.—Neurofibromatosis of right upper eyelid and right pulsating exophthalmos.

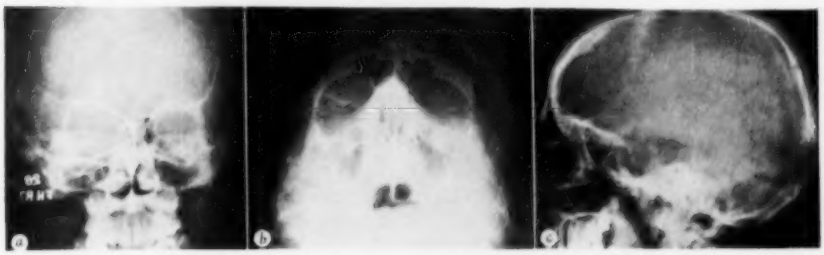

Fig. 10.—Enlarged right orbit, deformed anterior clinoid process, absent temporal line, forward enlargement of right middle fossa, and hypoplastic right anterior ethmoid cells.

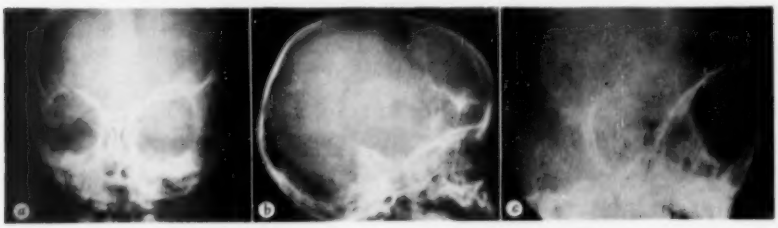

Fig. 11.—Enlarged left orbit, elevated sphenoid ridge, absent temporal line, and open sphenoid fontanelle, best seen in *c*, which was actually an optic-canal view for the right orbit.

It is of interest that the roentgenograms in this case are practically identical with those of Seaman and Furlow's [7] first case, in which the flared, open sphenoid fontanelle was also present. They referred to four similar cases in the literature, two of the patients having neurofibromatosis.‡ Although no mention was made of dermatologic findings of neurofibromatosis in the records of our Case 5, it should

‡ Recently, Dr. R. Storrs, of Syracuse, N. Y., acquainted us with an identical case, but without obvious neurofibromatosis.

be stressed that small nodular lesions were found in the supraclavicular regions and that it is quite possible for other stigmata of the disease to develop as the patient grows older.

CASE 6.—A 16-year-old girl (Fig. 12) had marked proptosis of the right eye and tremendous overgrowth of the soft tissues of the right upper lid and temporal region. The upper lid was pulled down onto the cheek. The temporal component of the mass had a raised, irregular, pigmented surface. On the trunk the patient had numerous café au lait areas and many small tumors. The dermatologist made the diagnosis of neurofibromatosis.

The beginnings of the disease of the eye had been noted at the age of 2 years, when it was thought the patient had a stye of the right upper eyelid. The lesion had grown progressively. At the age of 13 years biopsy of the temporal region had been performed, and the condition appeared to advance more rapidly after this.

Fig. 12.—Neurofibromatosis of the right orbit. See text for details.

Fig. 13.—Enlarged right orbit, elevated sphenoid ridge, absent temporal line, deformed sella and right anterior clinoid process, deepened right middle fossa, and small and opaque anterior ethmoid cells on right.

Roentgenograms of the head (Fig. 13) disclosed that the right orbit was much larger than the left. Its inferior border was scooped out, probably a result of the long-standing drag of the orbital contents on it. The temporal line was absent and the roof of the orbit deficient. The right anterior clinoid process was not seen, and the right side of the sella was deformed. The anterior ethmoid cells on the right were opaque and less well developed than on the left.

As a preliminary operation, the right external carotid artery was ligated. The eye was then enucleated, and a large degenerating neurofibroma, which lay behind the globe and which extended under the skin of the right temporal region, was removed.

COMMENT

The clinical history and roentgenologic findings in the cases presented appear to be so typical that the condition should not be readily confused with other entities. The main features in the clinical history are the presence of congenital unilateral exophthalmos, with or without pulsation; thickening of the upper lid, and sometimes also of the temporal region, and dermatologic stigmata of neurofibromatosis.

In some cases the progression of the upper-lid lesion and the proptosis may be at a catastrophic rate and result in monstrous deformity.[15] In other cases the condition appears to be relatively stationary over a prolonged time, for example, in Case 4.

Evidence of neurofibromatosis was present in five of our six cases, and in the other case (Case 5) it may have been of the forme fruste type. A neurofibroma of the orbit was present in the last case. It is known that manifestations of neurofibromatosis, such as café au lait areas and skin tumors, may appear only in late childhood, and even later. It should also be stressed that the absence of conventional findings does not negate a diagnosis of neurofibromatosis.

The roentgenologic manifestations of elevation of the sphenoid ridge, enlargement of the middle cranial fossa, elevation and deformity of the anterior clinoid process, and indistinctness or absence of the temporal line of the greater wing of the sphenoid may all be present in chronic subdural hematoma and chronic subdural hygroma.[16] But the association of other evidence of neurofibromatosis gives a definite and different significance to the roentgenologic findings in the cases described.

When the exophthalmos is of the pulsating type, and arteriovenous fistula or previous orbital operations for exophthalmos have been excluded, one may be certain that the cause of the pulsating exophthalmos is to be found in a deficiency of the bony structures at the apex of the orbit, with resulting encroachment by the temporal lobe of the brain and its coverings on the orbital contents. The pulsation of the brain is then transmitted to the structures in the orbit. Such a situation may appertain in cases of posterior orbital encephalocele [17] or in cases in which there is obvious neurofibromatosis, such as have been discussed in this paper. In this connection, it is tempting to speculate whether the cases of posterior orbital encephalocele are cases of incomplete neurofibromatosis, possibly similar to thoracic meningocele, which apparently bear a close relationship to neurofibromatosis.

SUMMARY

Six cases of congenital unilateral exophthalmos are presented. In five of the cases there was dermatologic evidence of neurofibromatosis. In three of the six cases the exophthalmos was pulsating. The roentgenologic appearance of the head is typical in these cases. It is interesting that the proptosis may or may not be accompanied by the presence of a retro-orbital neurofibroma. The mechanism of the pulsation is discussed.

The condition appears to be so characteristic that a mistaken diagnosis is unlikely once the clinical and roentgenologic pictures are known.

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LATE RESULTS OF PENETRATING KERATOPLASTY

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ALTHOUGH the literature dealing with corneal transplantation now includes more than 600 articles, adequate statistical evaluations of the late visual results of penetrating transplants are very few. Since the number of patients with ocular conditions requiring keratoplasty is relatively small, few ophthalmic surgeons have the opportunity of performing any large number of these operations. For the same reason, few surgeons are able to acquire the degree of technical skill and familiarity with complications in this operation which they are able to develop in procedures which they perform more frequently. This means that small groups of cases can at best have only a doubtful statistical value as concerns the final visual results. Larger, compiled series of operations which have been performed by a number of surgeons, in which each surgeon has contributed a few operations, are subject to the same criticism. The combined statistics are no less erroneous in the evaluation of the procedure simply because small series have been added together to produce a larger one. What kind of information would be gained about cataract extraction from a review of 500 operations, for example, in which 50 surgeons reported the first 10 operations they had performed?

In addition to the difficulty in evaluation due to differences in technical skill among surgeons performing a few transplants, there is a second difficulty, caused by differences in selection of cases and in indications for operation. Some surgeons feel that no patient with vision of 20/200 or better should have a corneal transplantation. Others, with greater confidence in the operation, are willing to operate on patients with vision of 20/50 if the circumstances seem to warrant it. Two series based on such divergent standards are not comparable as to visual results. Aside from the level of visual acuity, the selection of cases on the basis of favorability or unfavorability for operation will vary greatly with different surgeons and different clinics. In general, the selectivity of cases will tend to be less stringent in clinics where resident surgeons are undergoing training than it is in a private practice. In a clinic service operations will be done in more of the unfavorable, and even very unfavorable, cases, and this will be reflected in the final results.

With these factors in mind, some of the apparent discrepancies which have been noted in recent evaluations of the results of penetrating keratoplasty become entirely understandable, and there is no longer any necessity for assuming that one report is overly optimistic or that another is unduly destructive. To this should be added, perhaps, the common observation that all new or newly modified surgical procedures tend to pass through a familiar cycle of initial enthusiasm, followed by skepticism, then pessimism and debunking, and, finally, a rational evaluation and assignment to the surgeon's armamentarium.

REVIEW OF RECENT LITERATURE ON RESULTS OF PENETRATING KERATOPLASTY

Most of the earlier reports of the results of penetrating keratoplasky dealt with the transparency of the graft rather than the improvement in vision. The comprehensive review of the literature by Stansbury [1] summarized very adequately the reported visual results of keratoplasty through 1948. Incidence of improved vision varied from 12.5% (Filatov, 1935) to 46.7% (Elsching, 1930).

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In "favorable" eyes the percentage of success varied from 24.1 (Filatov, 1945) to over 90 (Castroviejo, 1939).

The symposium of the American Academy of Ophthalmology and Otolaryngology [2] in 1947 was an attempt to produce a critical evaluation of the results of corneal transplantation by compiling the statistics from seven clinics. Although the study has been criticized on other grounds, there are, as I have already pointed out, important objections to a compilation of this type, in which many surgeons contribute small numbers of cases. The total number of cases studied four months or longer was 381. The four-month period of observation is much too short, as will be pointed out later.

Of the 381 cases, clear grafts were present after operation in 63.5% and cloudy grafts in 36.5%. For the purpose of analyzing the visual result, cases with cataract, glaucoma, nystagmus, and amblyopia were eliminated from the series as introducing extraneous factors not pertinent to the results of the keratoplasty. Two hundred fifty-three cases were retained for analysis of the visual results. Of these, 79 cases were classified in Group I (favorable cases of keratoconus, central opacity, or mild interstitial keratitis). Fifty-eight of the patients had preoperative vision of 20/200 or less. Only 6 of this group had final vision of 20/30 or better; 32 (55.2%) had postoperative vision of 20/100 or better; 13 had less than 20/200 vision. On the basis of these statistics, the authors concluded that "the visual results in patients with preoperative vision of 20/100 or better do not warrant the risk of the operation." In prognostic Group II, that of moderately favorable cases, there was preoperative vision of 20/200 or less in 74. Vision was improved to 20/100 or better in 52.7%. In Groups III and IV, those of the least favorable cases, there was preoperative vision of 20/200 or less in 64. Improvement in vision to 20/100 or better occurred in 10.9%.

In the entire group of 253 patients, 229 had preoperative vision of 20/200 or less, and of these, 36.2% had final vision of 20/100 or better. Twenty-four patients had preoperative vision of 20/100 or better; of these, 13 were made worse after keratoplasty, with final vision of 20/200 or less.

Expressing dissatisfaction with the interpretation of the records supplied from the Institute of Ophthalmology, New York, Stansbury [1] again reviewed the operations from the ward services. This study consisted of 165 operations performed on 110 patients. The follow-up period ranged from 6 to 134 months. Vision was improved to 20/200 or better after 13% of the operations (16% of the 110 patients). There was no significant change in vision following 52% of the operations (42% of the patients). Loss of vision occurred after 35% of the operations (in 39% of the patients). Loss of light perception occurred in 12% of the series. In 3% the results were not known. In the most favorable group of cases (keratoconus) vision was improved in 10 out of 35 operations.

These figures present a very discouraging picture of keratoplasty, with 39% of patients losing vision after operation and only 29% of the most favorable group showing improvement. A more encouraging survey was presented at the International Symposium on Corneal Surgery [3] in April, 1949. This report dealt with the results in 100 cases of penetrating keratoplasty performed by R. T. Paton. It concluded that "without selection, in 55 percent of these cases, the result was clear grafts; 45 percent ended with cloudy grafts." The follow-up period was "four months or longer." Visual results were not given.

The comprehensive monograph published in 1948 by Paufique, Sourdille, and Offret [4] summarized the results in 172 cases of partial penetrating keratoplasty, among other types of keratoplasty. Cases were contributed by Sourdille (119), Paufique (32), Joseph and Offret (5), Legrand (8), and Jayle and Ourgrand (8). As in the statistics of Owens and associates,[2] 13 cases were eliminated from the analysis of the visual results because of cataract, vitreous opacities, or fundus lesions. The French authors do not accept the grouping of cases for prognostic purposes

which has been generally adopted in the United States. They divide their cases into three groups: Group I (traumatic keratitis) includes cases of chemical and physical injuries, burns, and traumatic ulcers. Group II (infectious keratitis) includes corneal ulcers; herpes; tuberculous, syphilitic, and rheumatic corneal lesions; trachoma, and corneal inflammations of unknown origin. Group III (degenerative keratitis) consists of cases of Groenouw's dystrophy, lattice-type dystrophy, bullous keratitis, keratoconus, and lipid dystrophy. It is apparent that cases of different prognostic categories have been grouped together in this classification.

In Group I (26 cases) the vision after keratoplasty was classed as improved in 38.5%; in Group II (104 cases), as improved in 52.9%, and in Group III (29 cases), as improved in 69%. The authors stated that "measurable" vision was obtained in 85 (53%) of the 159 cases.

Franceschetti [5] reviewed his results in 129 cases of penetrating keratoplasty. His Group I (favorable prognosis) includes cases of corneal degeneration, phlyctenular keratitis, and corneal alterations after glaucoma (40 out of 41 transplants were clear). Group II (uncertain prognosis) consists of cases of interstitial keratitis, herpetic keratitis, corneal infections in childhood, and corneal infections in adults (26 out of 58 transplants were clear). Group III (unfavorable prognosis) is comprised of cases of leucomas after severe injuries and corneal degeneration associated with aphakia (4 out of 30 transplants were clear). The visual results are not given in this article, but it is stated that functional improvement was obtained in 41% of 114 cases. The visual results in this group of 114 cases may be found tabulated in the monograph by Paufique and associates.[4]

In another article covering the same material [6] (129 cases) the operations are divided into nine categories for prognostic purposes. Only the transparency of the graft is used as a criterion of success; the visual results are not presented. In three categories (corneal degenerations, phlyctenular keratitis, keratoconus) the results were almost 100% successful. In four categories (interstitial keratitis, virus diseases, opacities due to infectious keratitis, and opacities due to keratitis in childhood) the chances of success are about 50%. In traumatic leucomas and corneal degeneration associated with aphakia, keratoplasty is almost always a failure.

Ciotola [7] reported the visual results of 40 partial penetrating grafts performed in the ophthalmologic clinic of the University of Rome. The grafts were all 4 to 5 mm. in size, were cut with the Franceschetti trephine, and were fixated by means of crossed sutures. He stated that transparent transplants were obtained in 60% of the cases of leucoma after infection, trachomatous pannus, keratoconus, and primary and secondary corneal degenerations. In parenchymatous keratitis 71% of the transplants, and in disciform keratitis 50%, were successful. No clear grafts were obtained in cases of chemical burns. Of the 40 cases, the postoperative visual acuity was 10/10 in 4, 10/10 to 5/10 in 12, 4/10 to 1/10 in 15, and less than 1/10 in 13.

Kurz [8] analyzed his results in 120 out of 150 penetrating keratoplasties performed between 1946 and 1949. The rest of the grafts had not been observed for a sufficiently long period. The technique employed was that of trephining, covering the graft with egg membrane, and fixating both with crossing sutures, as described by Tudor Thomas. Kurz grouped his cases in the manner used by Paufique and his co-authors. In Group I (traumatic keratitis) vision was improved in 27.7%; in Group II (infectious keratitis), in 35.5%, and in Group III (degenerative keratitis), in 42.1%. The final visual acuity was 6/6 to 6/36 in 35.8%, 6/60 to 2/60 in 18.3%, and not improved in 45.8%. Two operations ended in phthisis, and three resulted in total blindness from glaucoma. Kurz commented on the relatively poor results obtained in cases of parenchymatous keratitis, in which only 9 of 26 grafts remained clear.

Vanysek [9] reported briefly on 40 cases of keratoplasty, in 30% of which the grafts were clear. He stated that if primarily unsuitable cases were eliminated and only the suitable

were analyzed, the operation was successful in 48%, partially successful in 28%, and a failure in 26%.

A similar study of 45 cases of penetrating keratoplasty was made by François,[10] who described favorable results in 51% of his operations.

The most detailed recent report on the results of penetrating keratoplasty, and one of the most important because of the large number of operations performed by one surgeon, is that of Löhlein,[11] of Berlin. The article summarized the results of 286 operations in 225 patients. The visual results are analyzed in 241 operations, the remainder having been performed for tectonic or therapeutic purposes. It is to be regretted that the actual visual acuities are not reported, but cases are classified as "slightly improved," "definitely improved," "unchanged," "slightly worse," and "worse." The cases are grouped according to the etiology of the corneal damage into 14 categories (burns, explosions, infections, parenchymatous keratitis, degenerations, etc.). In the 241 cases analyzed for functional improvement, 14 eyes (5.6%) were completely lost and 26 (10.8%) suffered a less severe reduction in vision. In 73 (30.3%) there was no change. There was slight improvement in vision in 40 (16.6%) and marked improvement in 88 (36.5%). Summarization of these figures indicates that in 16.4% vision was worse after operation, in 30.3% unchanged, and in 53% improved.

PRESENT REVIEW OF CASES

Material.—This report is a review of the late results of 100 consecutive partial penetrating transplants (93 eyes) performed by me. The shortest period of observation in this group is 18 months and the longest 15 years. Thirty cases have been followed for 18 months to 2 years; 23, from 2 to 5 years; 28, from 5 to 10 years, and 9, from 10 to 15 years.

The opinion is generally expressed in the literature that corneal grafts which remain clear from four to six months may be considered permanently successful. While this is true in the majority of cases, the criterion is not acceptable for the purpose of a statistical review of the final visual results. A number of cases have been observed in which late edema of the transparent graft has appeared from 6 to 18 months after operation. For this reason, 18 months has been chosen as the minimal period of observation. The problem of this late clouding of the graft will be discussed further, under "Late Complications."

The inclusion of cases observed for a period shorter than 18 months would have produced a material increase in the percentage of successful cases.

Seventy-one of the operations were on private patients; 9 were on patients at the Eye Clinic of the Stanford University School of Medicine; 4 were performed at Letterman Army Hospital, and 16 were done at the Veterans Administration Hospital, San Francisco. In each case the examination and the selection of cases for keratoplasty were made by me. No cases were excluded from the series for any reason whatsoever. Cases with amblyopia, cataract, glaucoma, and other conditions influencing the visual results in the presence of a clear transplant were included. The presence, or possible presence, of such extracorneal disease should be recognized prior to keratoplasty. If, despite this knowledge, the patient is still accepted for keratoplasty, there is no more reason for excluding the case from statistics than there would be for excluding a similar case from statistics on cataract surgery.

The 100 operations reviewed were performed on 93 eyes in 80 patients. Thirteen patients had penetrating keratoplasty in both eyes; 8 of these had bilateral keratoconus; 2, phlyctenular keratitis; 2, Groenouw's dystrophy, and 1, central leucomas from interstitial keratitis. Five patients had two operations in the same eye, in an attempt to replace a cloudy graft with a second graft. One patient had three keratoplasties in the same eye. None of these seven secondary operations were successful.

Preparatory Treatment. — Preparatory treatment was undertaken in eight cases. This consisted of superficial keratectomy followed by irradiation for reduction of vasculariza-

tion in three cases, of irradiation alone in three cases, of preliminary iridectomy in one case, and of cauterization of an extremely conical cornea to flatten it in one case. The use of soft x-rays and beta radiation was restricted to corneas showing extreme degrees of vascularity. A moderate or slight degree of vascularity was not considered a contraindication to keratoplasty, and it was felt that it is wiser to reserve such irradiation for the postoperative period, if necessary, since newly formed capillaries are much more sensitive to radiation than are larger, established blood vessels. It is my feeling, at present, that very few patients are benefited by lamellar keratectomy and/or irradiation in preparation for penetrating keratoplasty. Very superficial keratectomy, such as is represented by the removal of a pseudopterygium or vascularized membrane covering the cornea, is very useful. Actual lamellar resection, however, leaves the cornea thin and in poorer condition for a penetrating graft. It has also appeared to me, not only on the basis of the few patients treated in this series but from observation of many others treated by irradiation for reduction of vascularity prior to keratoplasty, that the heavy irradiation necessary to destroy or attenuate old blood vessels leaves the cornea in a devitalized state, which is unfavorable for transplantation. For this reason, I have preferred to control bleeding from corneal vessels by peritomy or diathermy coagulation at the limbus at the time of operation, and to withhold irradiation until the postoperative period, when the newly formed vessels may be destroyed by a much smaller dose.

Indications for Operation.—Two general considerations guided the selection of cases for operation: (1) the patient's need for improved vision and (2) the possibility of improvement. The level of the visual acuity was not used as an absolute factor. Three patients (two with keratoconus and one with interstitial keratitis) had preoperative vision of 20/70. Seven patients had preoperative vision of 20/200. In the remaining 90 cases the preoperative visual acuity was less than 20/200. In 27 of 37 eyes with keratoconus, the visual acuity could be corrected to 20/50 or better with contact lenses, but the patients were unable to wear the contact lenses for sufficiently long periods. The eye undergoing keratoplasty was an only eye in 11 patients, the fellow eye having been enucleated or else lacked light perception (epithelial dystrophy with mature cataract, 1; dystrophy with aphakia, 1; perforating injury to the cornea and lens, 1; exposure keratitis with malignant exophthalmos, 1; Groenouw's dystrophy, 1; explosion injuries with aphakia, 2; chemical burns, 4).

The fellow eye was normal in 10 cases. These cases included five of industrial accidents in which maximal restitution of vision was requested by the injured, 1 of descemetocele in a central leucoma, 2 of recurrent herpetic keratitis, and 2 of young patients who desired operation for cosmetic reasons as much as for visual reasons. The ages of the patients varied from 14 to 66. The majority were in the age period of 25 to 45. Only three patients were under 20 years of age. There were 22 women and 58 men.

Technique of Operation.—Although numerous minor technical modifications were employed at various times, the 100 operations may be divided in four general types.

1. In 74 cases the square transplant was performed, with use of the double knife and scissors of Castroviejo, with overlying fine silk sutures anchored in the recipient cornea. The fixation sutures were of either the Tudor Thomas[12] or the Castroviejo[13] pattern and were inserted in the recipient cornea 0.5 to 1 mm. from the wound edge. The size of these square grafts varied from 4 to 7 mm., the majority being 6 to 6.5 mm.

2. In two cases a 6.5 mm. square transplant was used, but fixation was obtained by means of 12 direct appositional sutures.

3. In seven cases a round transplant, obtained by means of the manual trephine, fixated by two figure-of-eight sutures crossing over the graft, was employed.

4. In 17 cases a round transplant, 7 to 10 mm. in size, was used, absolute fixation being obtained through the use of 12 to 16 direct appositional sutures, depending on the size of the graft. In this technique four to eight of the sutures are preplaced in the transplant before it is excised from

the donor eye. The Castroviejo trephine, with an inside stop, is used to penetrate the donor cornea to a depth of 0.4 to 0.6 mm. Double-armed 00000 nonabsorbable (silk) surgical sutures mounted on sharp cutting needles (Grieshaber or similar type) are inserted 1 mm. inside the incised border of the graft and brought out through the incision, much as in preplacing sutures for a cataract operation. One needle of each double-armed suture is inserted at either end of the vertical and horizontal meridians, the silk forming a cross over the graft. With larger grafts two additional double-armed sutures are inserted in the oblique meridians. The anterior chamber is then punctured through the trephine incision with a sharp discission knife, and the graft, together with the preplaced sutures, is excised by means of corneal scissors. After excision of the corneal disc from the recipient, the graft is dropped into position and the needles are inserted in the recipient cornea at points corresponding to the position of the sutures in the graft. The sutures are then cut over the center of the transplant and tied so that each of the double-armed sutures has provided two direct sutures. With four to eight of the sutures preplaced in this manner, trauma to the graft from instruments is minimized. Additional direct sutures are placed as is necessary to produce a watertight closure, usually 12 to 16 in all. Further details of this technique will be described in another publication.

Donor Material.—In approximately 15 operations the source of the corneal graft was an eye enucleated for a tumor in the posterior segment. In five operations the corneal graft was obtained from an eye enucleated for absolute glaucoma. Such corneas from enucleated eyes were transplanted from a few minutes to a few hours after the eye was removed. The remaining transplants were obtained from cadaver eyes removed two to eight hours after death. These eyes were suspended in a ring in an airtight bottle containing a piece of moist gauze to provide a moist atmosphere and were placed in the refrigerator at a temperature of 2 to 6 C. until the cornea was used. Practically all operations were performed within 24 hours after the death of the donor. In a few cases the eyes were used from 24 to 36 hours after death.

Complications.—The principal immediate postoperative complications encountered in this series of cases were iris adhesions and secondary glaucoma. Anterior adhesions between the iris and the operative wound caused by delayed filling of the anterior chamber occurred after 10 operations. In five of these cases anterior synechia had been present prior to keratoplasty and had been separated at the same time that the keratoplasty was performed. In 5 of the 10 cases with postoperative anterior synechiae, the adhesions were freed with a blunt spatula, either through a cyclodialysis incision or through a small corneal incision. In the other five cases the synechiae were peripheral and were permitted to remain, since they did not appear to influence the fate of the graft. Since the adoption of direct suturing, iris adhesions are a less serious problem.

Glaucoma following keratoplasty was observed in 10 cases. In half of these secondary glaucoma was known to have been present at some time prior to the corneal transplantation but appeared to have subsided. In the other five cases the glaucoma was definitely the result of the operative intervention. The glaucoma was controlled after cyclodialysis performed several weeks after keratoplasty in six cases. It subsided spontaneously under medical treatment in one case. In one case a malignant glaucoma developed 48 hours after keratoplasty and required resuturing of the transplant, iridectomy, extraction of the lens, and a cyclodiathermy before the glaucoma was brought under control. This eye, which had a preoperative vision of hand movements, was left with visual acuity of 20/400. In the remaining two cases the prognosis for vision was so poor that the glaucoma was permitted to continue without treatment. One was a case of injury complicated by severe uveitis, vitreous opacities, and optic neuritis. The other was a case of aphakia with corneal dystrophy in an elderly patient, in which keratoplasty was undertaken as a means of temporary improvement in vision, with the knowledge and acquiescence of the patient.

The important later complications were late opacification or edema of the graft, and ectasia of the graft.

Late clouding of the graft occurred in 24% of the operations. This little-understood

disturbance of the transplant appeared at intervals of 3 weeks to 18 months after keratoplasty.* At the time of onset, the graft, which had appeared lustrous and transparent, although possibly slightly thicker than a normal cornea during the first month after operation, suddenly became hazy and edematous, and the epithelial surface lost its luster. Fine folds appeared in Descemet's membrane. With the slit lamp the endothelial surface was noted to have lost its smooth and regular pattern. In the majority of cases the edema involved the entire transplant, but in a few only the central portion of the graft, or only one sector of the transplant, was so affected. A fine opacification could usually be observed in the zone of Bowman's membrane overlying the area of stromal edema. In those cases in which only a portion of the graft was involved, the corresponding area of endothelium was affected, and this was frequently demarcated from the normal-appearing endothelium by a fine, chain-like, brownish-gray deposition of cells. These lesions never appeared to have the color of fresh K. P. When only the central portion of the graft was involved, this deposit on the endothelial surface at times formed a complete or a broken ring, which could be observed for several months after the process had subsided. No rapid vascularization of the graft was noted in association with this condition. If the edema persisted for many weeks, a very slow encroachment of vessels from the line of union of the graft and the recipient took place, when vessels were present at that site prior to the onset of the edema. In several cases in which the edema persisted for several months the graft never became vascularized. I was not able to establish any correlation between the presence of blood vessels in the cornea adjacent to the graft and the occurrence of this late edema. In three patients with this complication it was definitely established after repeated slit-lamp examination that the surrounding cornea was completely devoid of vessels. The growth of vessels toward and into the graft appeared to take place as a response to the edema, when it did occur.

One of the most striking features of this complication was the mild inflammatory reaction associated with it. In most instances there was only a slight conjunctival flush, which could be blanched quickly with epinephrine. There might be mild to moderate photophobia but no pain or tenderness. The aqueous usually was clear; in several cases a rare cell aggregate could be found, but rather inconstantly. No aqueous ray was observed. The iris took little part in the reaction. Frequently it appeared slightly edematous and the pupil somewhat sluggish, but in every instance the pupil could be dilated promptly with homatropine or scopolamine. Most striking of all was the complete absence of any reaction in the clear cornea around an edematous graft. This could be observed particularly well in cases of keratoconus, in which the graft was surrounded by transparent cornea.

The onset of the late clouding took place in the third to the sixth postoperative week in 12 of the cases. In 10 cases it appeared between the 6th and the 20th week. The onset was in the 6th month in one patient and in the 13th month after operation in another. In the last instance minor recurrences took place until 18 months after operation. In general, the prognosis for reversal of this late clouding seemed to vary inversely with the time of onset; that is, the later the onset, the prompter and more complete was the subsidence of the process. In all but 6 of the 24 cases of late edema recovery occurred, with more or less complete restoration of transparency. In a few, some fine subepithelial and stromal opacities could be found with the microscope months later. Three eyes continued to show a mild chronic edema two to four years after the operation. Three others recovered from the edema but were left with nebulas of the graft, which reduced visual acuity.

The course of the late edema was extremely variable in duration, lasting from a

* In a case of keratoconus observed since preparation of this report, clouding of a perfectly transparent graft appeared two years after operation. It cleared completely in two weeks.

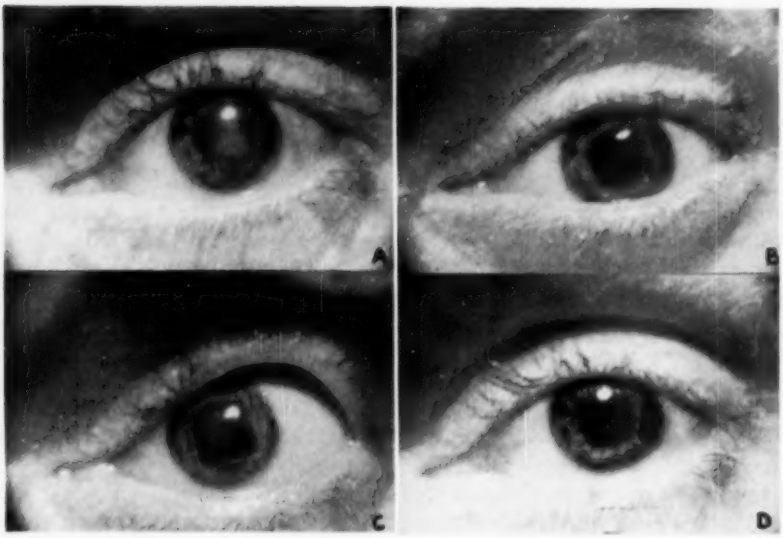

Fig. 1.—Late edema of corneal transplant (Case 67). *A*, opacity from disciform keratitis; *B*, clear transplant one month after operation (V 20/20); *C*, severe edema of the graft six weeks after operation; *D*, edema subsided, small residual opacity, after one year (V 20/30).

Fig. 2.—Late edema of transplant (Case 33). *A*, keratoconus with large central opacity; *B*, clear graft 6 months after operation (V 20/25); *C*, onset of edema 13 months after operation; *D*, graft clearing after 5 days' treatment with topical cortisone (V 20/20).

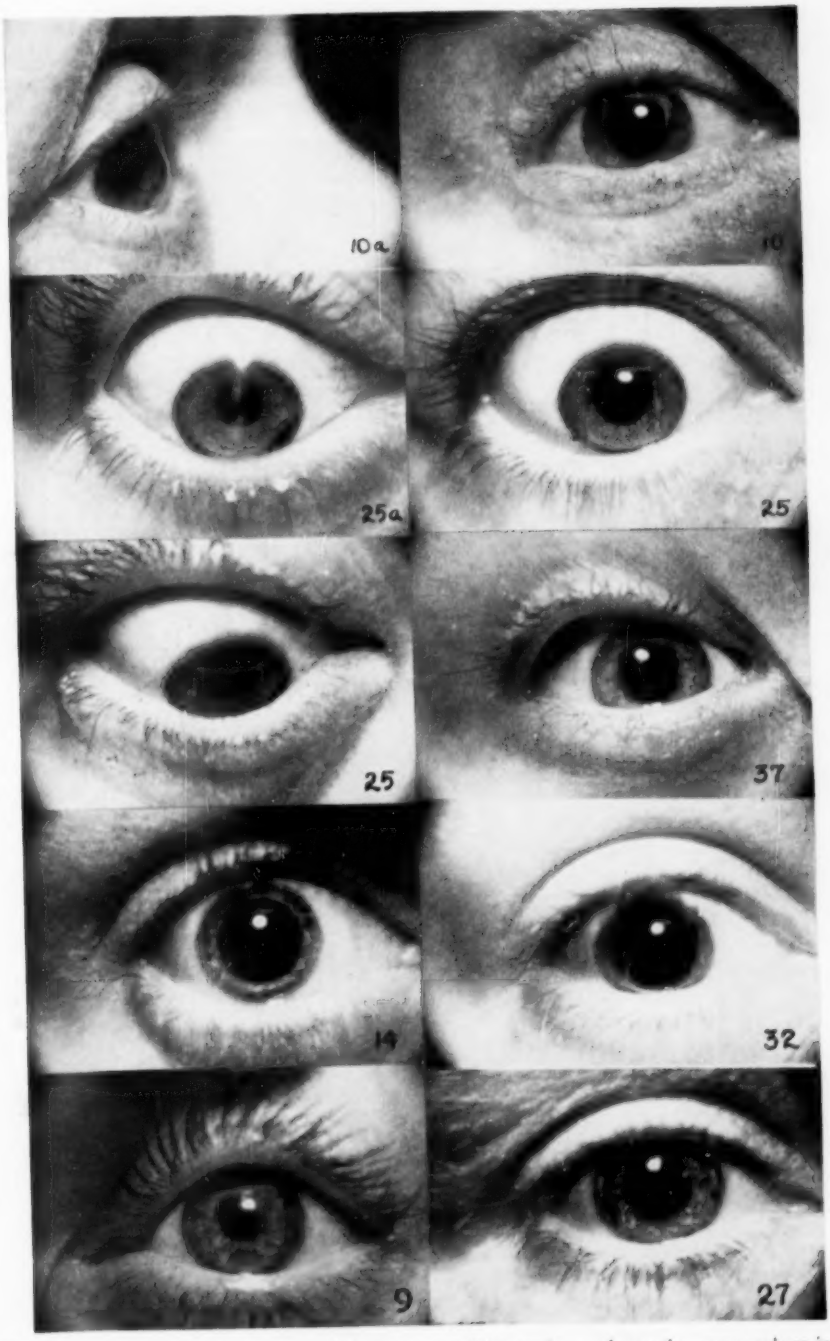

Fig. 3.—Square transplants in cases of keratoconus. The numbers refer to the case numbers in Table 6; *a* indicates preoperative appearance.

few weeks to 12 months in the cases in which there was final recovery. The earlier patients were often treated with soft x-rays, because it was thought that the presence of blood

Fig. 4.—Round transplants in cases of keratoconus; 8 mm. grafts with 12 direct, appositional sutures. The numbers refer to the case numbers in Table 6; *a* indicates the preoperative photograph.

vessels about the graft, and their tendency to enter the graft when the edema occurred, indicated a possible causal relationship. It is probable that nothing was achieved by this mode of therapy. Cortisone and hydrocortisone used topically, on the other hand, appeared to influence the process very favorably. In several patients with a late onset of the edema the topical use of cortisone has brought about complete disappearance of the edema within three to five days; conversely, its withdrawal has been followed by prompt

relapse. For this reason, I now advise such patients to continue the topical use of hydrocortisone two to three times daily for at least six months after the onset of late edema (Figs. 1 and 2).

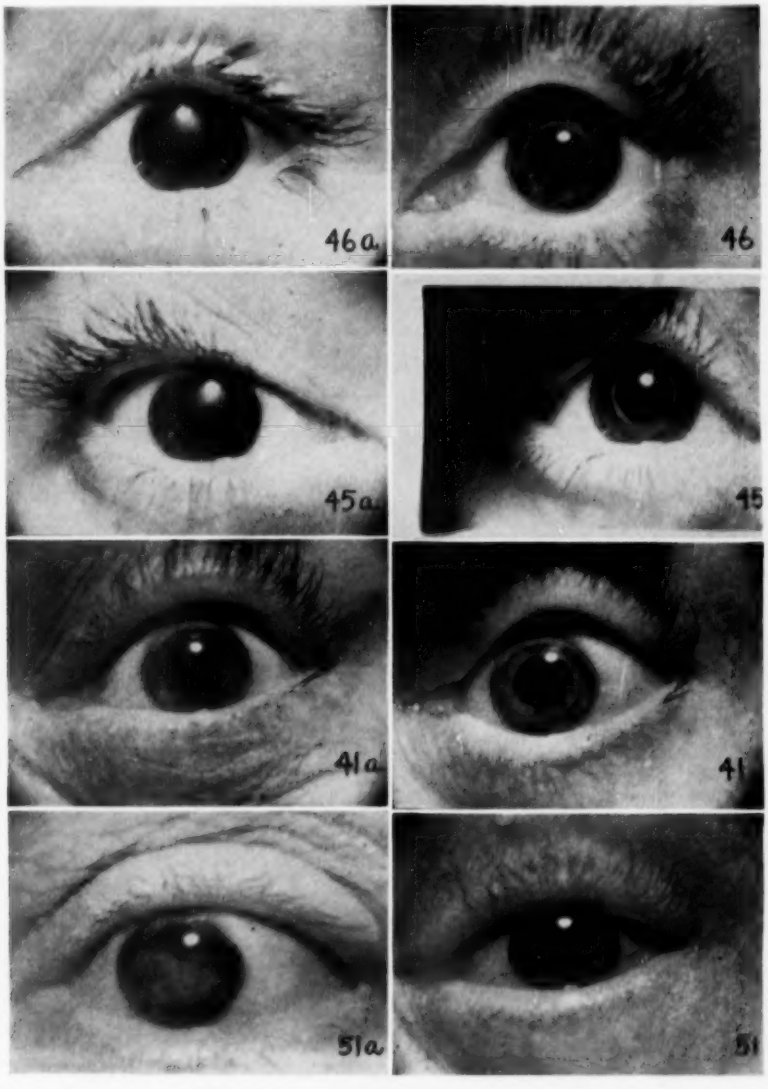

Fig. 5.—Corneal transplants in cases of opacity from interstitial keratitis. The photographs on the left are preoperative. The numbers refer to case summaries in Table 6.

Many theories have been proposed to explain this peculiar reaction—nutritional, infective, allergic, degenerative—but none provides an answer to all the problems. The most acceptable theory, taking into account most of the unusual features of the disease which have been described above, is that it is a form of endothelial dystrophy which has as its basis an antigen-antibody reaction in

the stroma of the graft. This problem is the most pressing in keratoplasty today, since it affects one out of four patients, and the most favorable cases equally with the less favorable.

Ectasia of the transplant may come about in one of two ways: There may be poor coaptation of the graft and the recipient cornea smoother and less prominent, but the graft has acquired a curvature which is much sharper than that of the surrounded cornea, and at the same time is usually irregular. A high degree of compound myoptic astigmatism or, more frequently, a high degree of irregular astigmatism may be present, so that the visual acuity cannot be brought to

Fig. 6.—Corneal transplants in circumscribed leucomas.
Tuberculous deep keratitis (Case 75); total adherent leucoma after infected foreign body (Case 63); adherent leucoma after perforated ulcer (Case 59). The letter *a* indicates preoperative photograph.

primarily, either in one sector or about the entire circumference, so that the graft is elevated slightly above the level of the recipient cornea. Occasionally the graft may be in contact with the recipient only through the deepest layers of the stroma. In time the difference in levels tends to disappear, as epithelial cells fill the step on the surface and fibrous tissue is proliferated more deeply. After many months the line of union becomes more than 20/200 or so except with a contact lens.

In another group of cases, coaptation of the borders may be good but, because of the thinness of the recipient cornea or of the graft or of both, the line of union is not strong. The visual result may be excellent during the first few weeks after operation, but as months go by it is observed that an increasing degree of myopia or compound

myopic astigmatism appears, much as though a conical cornea were developing. In such cases the visual acuity can usually be corrected to a useful level with ordinary glasses, but the lens required may become extremely strong.

In three cases in which ectasia of the graft was associated with poor coaptation of the edges around half the circumference, I was able to remedy the condition in the following way: Five to 10 weeks after keratoplasty, when the line of union had become fairly strong, the epithelium was curetted from the ectatic portion of the border. The line of union was punctured with a sharp discission knife at the point where the poor approximation of the edges seemed to begin, and the portion of the line of union which was in poor position was cut with scissors until one-half to two-thirds of the circumference was free. The edges were then reapproximated with direct sutures placed at intervals of 2 mm. and tied with slight tension to produce a flattening of the transplant. The anterior chamber refilled promptly, and reaction in the eye and in the graft was minimal. The sutures were removed after three weeks, and in each instance there was appreciable improvement in vision (20/40, 20/50, 20/50) with glasses.

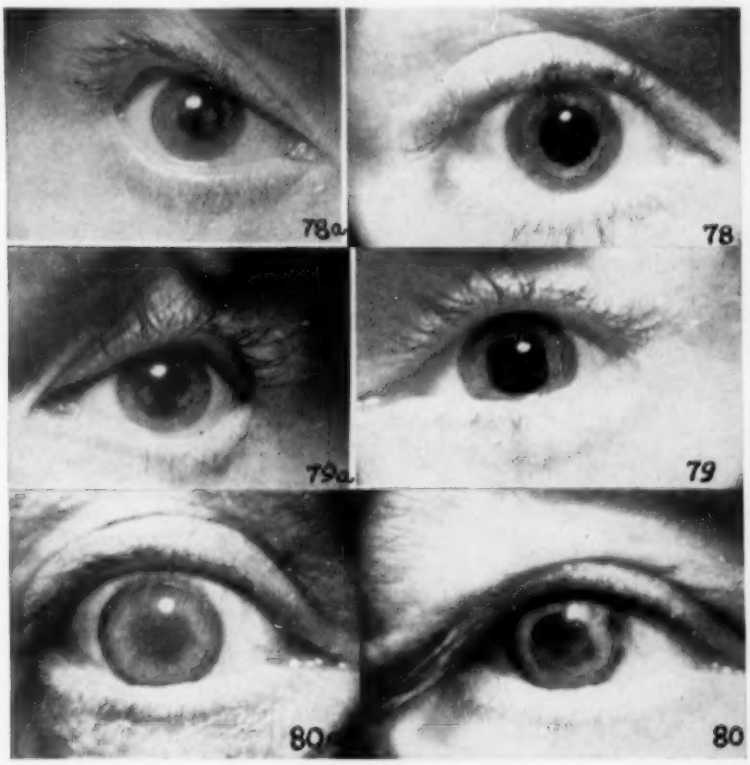

Fig. 7.—Corneal transplants in cases of Groenouw's dystrophy. The numbers refer to the case numbers in Table 6, and *a* indicates preoperative photographs.

Ectasia of the transplant and consequent high refractive errors were encountered most frequently in severe cases of keratoconus in which the cornea surrounding the graft was soft and thin. The correcting lenses required to achieve maximal visual acuity after kera-

toplasty are recorded in the summarization of cases (Table 6) and furnish an adequate guide to the incidence and degree of ectasias.

Results.—The final results of the 100 operations in terms of visual acuity, as well as of transparency of the graft, are summarized in Table 6. In addition to a record of the vision before and after operation, there is also a notation as to whether the operation improved vision, left it unchanged, or made

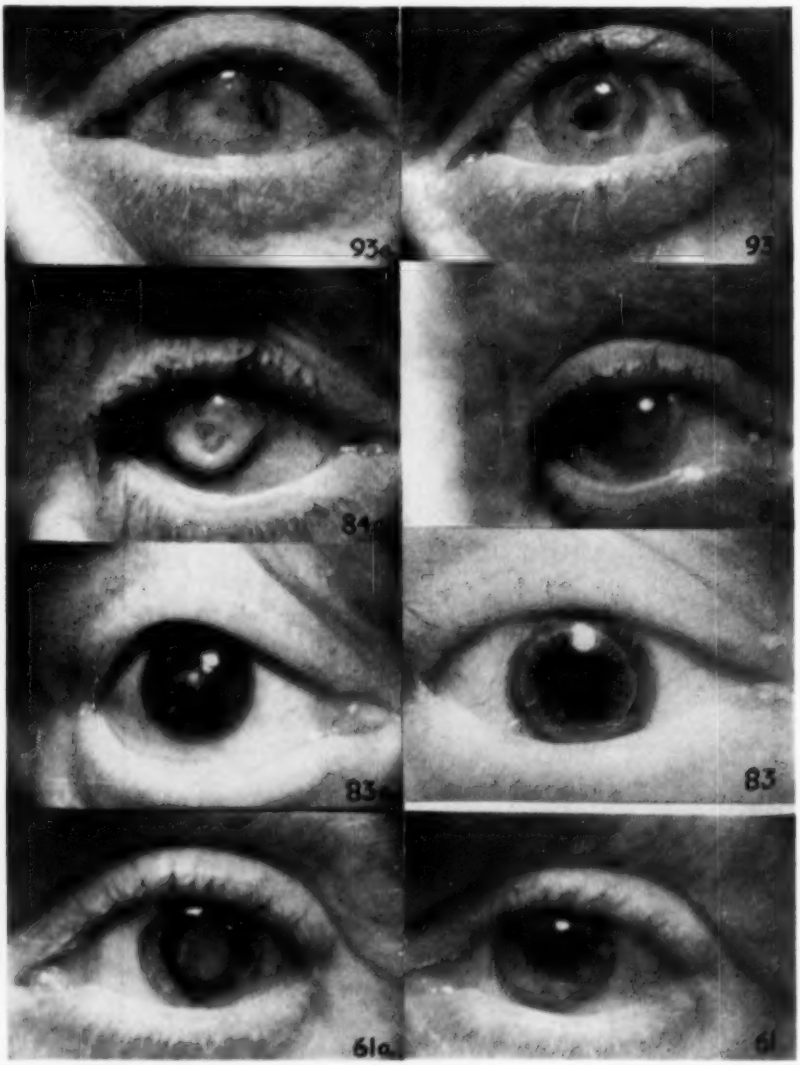

Fig. 8.—Transplants in association with aphakia.
Case 93: Adherent leucoma and aphakia after perforation by nail.
Case 84: Pitting edema of cornea and aphakia after complicated cataract operation and uveitis. Total transplant partly clear.
Case 83: Fuchs's dystrophy, mature cataract. Cataract extraction done eight months after grafting of large transplant.
Case 61: Leucoma after infection. Lens removed at time of transplantation because of injury to capsule.

TABLE 1.—*Visual Results of Penetrating Keratoplasty in One Hundred Cases*

	No.
Improved (increase of 2 steps or more in the visual scale)	74
Not improved (increase of less than 2 steps in visual scale)	16
Worse	10

TABLE 2.—*Analysis of Seventy-Four Cases Improved by Penetrating Keratoplasty*

	No.
Vision 20/20 to 20/40 (good)	41
Vision 20/50 to 20/100 (fair)	19
Vision 20/200 or less (poor)	14

TABLE 3.—*Cases Improved by Penetrating Keratoplasty*

		Visual Result			
	No. Cases	Good (41)	Fair (19)	Poor (14)	Total Improved
Keratoconus	37	26 (70%)	8	1	35 (95%)
Interstitial keratitis	14	4	3	4	11 (79%)
Leucoma following infection	12	3	2	2	7 (58%)
Groenouw's dystrophy	5	2	2	1	5 (100%)
Phlyctenular keratitis	5	2	1	1	4 (80%)
Disciform keratitis	4	1	2	1	4 (100%)
Blast injury	4	..	1	2	3 (75%)
Fuchs's dystrophy	2	1	..	1	2
Leucoma, traumatic	2	1	..	1	2
Keratitis, T.b.	1	1	..	..	1

TABLE 4.—*Analysis of Sixteen Cases Not Improved by Keratoplasty*

	No.
Secondary operations (Cases 96, 97)	2
Dense vascular leucomas (Cases 50, 54, 55, 60, 86)	5
Severe chemical burns (Cases 89, 90, 91)	3
Trachomatous keratitis (Cases 73, 74)	2
Clear grafts with amblyopia (Cases 39, 58, 70)	3
Late edema with opacification	1
Malignant exophthalmos (exposure keratitis; Case 57)	1

* Numbers refer to case numbers, Table 6.

TABLE 5.—*Analysis of Ten Cases Worse After Keratoplasty*

	No.
Secondary operations (Cases 94, 95, 98, 99, 100)	5
Partial extrusion with opacification (Case 16)	1
Expulsive choroidal hemorrhage (delirium) (Case 40)	1
Dystrophy invading graft (Cases 81, 82)	2
Death from pulmonary embolism (Case 23)	1

* Numbers refer to case numbers, Table 6.

it worse. It has been suggested that a fair standard of improvement in vision would be an increase of two steps or more in the visual acuity scale. This standard has been adopted in this summarization, with one modification. In those cases in which the visual acuity before operation is as low as light perception or hand movements, I believe that an increase to finger counting represents a definite improvement. Such patients are often made more self-sufficient by this modest increase in vision and are frequently more grateful than a patient whose vision has been improved from 20/70 to 20/50. In this series of 100 operations there were 21 cases in which the preoperative vision was only light perception or hand movements. In 12 of these vision is recorded as improved by the standard noted above, the postoperative acuity ranging from 20/20 to finger counting.

In the entire series there were 14 cases with postoperative vision of 20/200 or less which were classified as "improved (poor)." Since there may be some question as to whether or not such cases should properly be classified as improved, these 14 cases are listed here by number, as they appear in Table 6: Cases 22, 42, 44, 45, 48, 58, 62, 66, 72, 80, 74, 85, 88, 93.

If one feels that these cases do not belong in the category of "improved," they may be shifted to the category "not improved." The cases described as "improved" have been further divided into the visual classes "good," "fair," and "poor." The term "good" refers to those with postoperative vision of 20/20 to 20/40; the term "fair" is applied to those in which the postoperative vision was between 20/50 and 20/100, and the term "poor" applies to those in which the final vision was 20/200 or less—the 14 listed above (Table 6).

The refraction given is the refraction found at the time of the latest follow-up examination and represents the lens correction which provided the maximal visual acuity, rather than the measurement found on the keratometer, insofar as the astigmatic error is concerned. In many instances a spherical equivalent or a partial equivalent was found to give better vision than could be obtained with the astigmatic correction as determined by retinoscopy or ophthalmometry.

In six patients the visual acuity after operation is recorded with regular glasses and with the contact lens. These were patients who could wear contact lenses satisfactorily and whose vision could not be corrected to the maximum without them. Three of these patients achieved improvement in vision without a contact lens on the basis of the standard described above, but their vision was further improved by use of a contact lens. In the other three vision was not improved two steps in the visual scale with ordinary glasses, but could be improved with a contact lens, and they could wear it satisfactorily. There were a few patients whose vision could be improved further by a contact lens but who could not wear such a contact lens satisfactorily. Only the visual acuity with regular glasses is given for these.

On the basis of the standards described above, 74 of the 100 consecutive operations resulted in improvement in vision; 16, in no improvement, and 10 made the condition worse (Table 1). The cases in which vision was improved by keratoplasty are broken down etiologically in Table 3. These results, in general, are in close agreement with those described by previous authors.

Keratoconus cases appear to be in a class by themselves so far as the proportion of excellent visual results (70%) is concerned. For no other types of opacity in this series do values approach this figure, although improvement in vision of some degree was obtained in all cases of Groenouw's dystrophy, phlyctenular keratitis, and circumscribed opacity after disciform keratitis. Of 37 patients with keratoconus, 35 were improved in vision. Thirty-three of the 37 patients achieved a postoperative acuity of 20/100 or better with correcting glasses, and 26 had final visual acuity of 20/40 or better. The two keratoconus patients not recorded as improved are listed in Table 5 as among those made worse. One was an unruly patient

in whom a partial extrusion of the graft was produced by unmanageable blepharospasm. A second and a third transplantation were performed, but vision was lost as a result of secondary glaucoma. The second patient was a man of 24 who died suddenly of a pulmonary embolus on the 20th day after operation. This patient had had a completely negative medical history. The corneal transplantation was without complication, and he was permitted to rise from bed on the eighth day. At this time a small, warning pulmonary infarct occurred. The source of the embolus could not be determined. Recovery from the first embolism was prompt, and the patient appeared to be doing well, when the sudden fatal embolism occurred. The source of the embolus was found at autopsy in the deep iliac vein.

The results in cases of interstitial keratitis were excellent so far as the number of cases (79%) with improved vision goes. However, only four patients in this group attained visual acuity of 20/40 or better. Two patients with clear grafts but with partial amblyopia were encountered.

The group described in Table 3 as "leucoma following infection" is a somewhat heterogenous one. It includes various types of opacities after corneal infections. In three cases there were circumscribed central opacities with little vascularity, a condition which should be considered favorable from a prognostic point of view. Three were of adherent leucomas following perforated corneal ulcers with varying degrees of vascularization. One case of leucoma with a descemetocele is included. There were three cases of diffuse corneal opacification following herpetic lesions (not disciform) and two cases of leucoma in an aphakic eye.

The remaining etiological categories in Table 3 comprise only a few cases and are self-explanatory.

In Table 4, of cases in which vision was not improved by keratoplasty, are listed 16 operations in which the vision after operation was unchanged. This group includes the cases which are unfavorable, or relatively unfavorable, for penetrating keratoplasty, i.e., those of dense vascular leucomas, severe chemical burns, trachomatous keratitis, exposure keratitis, and retransplantation. The two cases of trachomatous keratitis are worthy of special notice. In each of these a small chronic fistula developed in the line of vision between the graft and the recipient which had to be closed secondarily. These were the only two cases in which this complication was encountered. Since only two cases are involved, this may well be a coincidence, but it is also possible that the diseased state of the epithelium in trachoma may lead to defective healing of the corneal wound.

The 10 cases in which vision was made worse after operation are extremely interesting. Of prime importance is the fact that five of these were cases of retransplantation. The conditions existing in the anterior segment after a transplant has become opaque are usually such that a subsequent transplant is also doomed to failure. Frequently the cause of opacification in the first graft is the fact that the condition of the cornea is one which is unfavorable for penetrating keratoplasty. It becomes no more favorable with the second or third operation. On the contrary, there may be increased vascularization, edema, and iris adhesions resulting from the first operation, which make the success of subsequent operations even more doubtful. Occasionally after a well-performed transplantation in a favorable case, one of keratoconus, for example, the graft may become cloudy or ectatic and may be replaced successfully. Such cases are infrequent, however. The great majority of retransplantations reported in other series have been failures, just as have the seven in this series.

The two cases in which an unclassified dystrophy invaded the graft are worthy of comment. One was that of a woman aged 30; the other, that of a man aged 20. In each case opacity of both corneas had been present since birth or infancy and had increased very slowly. On biomicroscopic examination the opacity was found to be made up of innumer-

TABLE 6.—*Summary of Case Histories**

Case No.	Patient	Sex	Age, Yr.	Diagnosis	Follow-Up, Yr.	Vision and Refraction		Visual Result			Final State of Graft	Complications	Comment †
						Preoperative	Postoperative	Improved	Not Improved	Worse			
							Primary Transplants						
1	R. A.	F	17	Keratoconus	2	10/400 C. L. = 20/100	20/40 — 1.00 ⌒ + 5.00 x 15	+	..	..	Faintly nebulous	Late edema of graft at 3 mo.	Cleared in 5 mo.; local cortisone
2	F. A. R. E.	F	32	Keratoconus	9	20/600 — 16.00 ⌒ — 5.50 x 160	20/40 — 2.00 ⌒ + 2.50 x 45	+	..	..	Partly nebulous	Late edema at 4 wk.; moderate vascularity	Cleared in 5 mo.; 1,500 r contact x-ray therapy
3	..... L. E.	..	..	Keratoconus	8	20/200 — 15.00 ⌒ — 4.00 x 150	20/70 — 7.50 ⌒ — 2.50 x 135	+	..	..	Faintly nebulous	Late edema at 3 wk.; moderate vascularity	Cleared in 4 mo.; 1,000 r contact x-ray
4	H. A.	M	33	Keratoconus	13	5/200 (C. L. = 20/200)	20/200 (C. L. = 20/30)	+	..	..	Clear	Small graft (4.5 mm. square) is flat, but cornea is more ectatic	Wears C. L. 8-10 hr.; ectasia of cornea about graft cleared
5	D. B.	M	61	Keratoconus	6	20/400 (C. L. = 20/200)	20/40 — 3.50 ⌒ — 3.50 x 115	+	..	..	Clear	.....	.....
6	E. C. R. E.	M	28	Keratoconus	3	20/400	20/70 — 6.00 sph	+	..	..	Clear	.....	Extreme keratoconus
7	..... L. E.	..	..	Keratoconus	4	1/200	20/60 — 6.00 sph	+	..	..	Clear	.....	Extreme keratoconus
8	R. C.	F	28	Keratoconus	8	2/200 + 5.25 cyl x 30	20/25 — 6.00 ⌒ — 2.50 x 135	+	..	..	Clear	Small iris adhesion separated 3 wk. post-operative	.....
9	R. D.	M	30	Keratoconus	3	20/800 (C. L. = 20/200)	20/40 — 1.50 ⌒ — 5.00 x 165	+	..	..	One corner hazy	Late edema at 2 mo., upper half only; secondary glaucoma	Cleared in 2 mo.; glaucoma controlled by cyclodialysis
10	M. E.	F	43	Keratoconus	2	1/200	20/30 — 6.00 sph	+	..	..	Clear	.....	.....
11	A. F. R. E.	M	..	Keratoconus	9	2/200	20/20 — 0.50 ⌒ — 2.50 x 125	+	..	..	Clear	.....	.....
12	A. F. L. E.	..	..	Keratoconus	8	2/200	20/25 — 3.50 ⌒ — 6.50 x 137	+	..	..	Clear	.....	.....
13	G. F.	M	28	Keratoconus	6	1/200	20/100	+	..	..	Nebulous	Severe late edema at 1 mo.	Partial clearing in 4 mo.
14	R. F. R. E.	M	19	Keratoconus	8	20/400	20/25 — 4.25 ⌒ — 2.50 x 150	+	..	..	Clear	Secondary glaucoma (trephine operation, age 16)	Glaucoma controlled by cyclodialysis
15	..... L. E.	..	..	Keratoconus	1½	20/70 + 1.75 ⌒ — 2.00 x 70	20/25 + 2.00 ⌒ — 3.50 x 110	+	..	..	Clear	.....	.....
16	V. G.	M	26	Keratoconus	8	1/200	H. M.	..	..	+	Opaque	Lower half of graft protruded at 1 wk.; iris adherent	Second transplant after iridectomy
17	R. H. (VAH) R. E.	M	21	Keratoconus	1½	20/400	20/20 — 1.50 ⌒ + 4.50 x 90	+	..	..	Clear	Mild late edema	Cleared in 2 mo.; topical cortisone
18	..... L. E.	..	..	Keratoconus	2½	20/400	20/25 — 2.00 ⌒ + 4.50 x 105	+	..	..	Clear	Late edema; severe, at 3 mo.	Cleared in 6 mo. after 3 recurrences; topical cortisone

19	R. N. K.	M	32	Keratoconus	3	20/800	20/25 + 0.50 ⌒ + 2.50 x 75	+	..	..	Clear	.....	.....
20	A. K.	M	50	Keratoconus	2	1/200	20/60 — 2.50 ⌒ — 7.50 x 165	+	..	..	Clear; sl. ectasia	Mild late edema at 3 wk.	Cleared in 3 mo.
21	S. L.	F	53	Keratoconus	2	1/200	20/30 — 3.00 ⌒ — 2.50 x 30	+	..	..	Clear	Hemorrhage into anterior chamber 6th postoperative day	1 mm. hole present in iris (surgical trauma)
22	L. L.	M	32	Keratoconus	3	20/800 (C. L. = 20/50)	20/80 — 2.00 ⌒ + 6.00 x 95 (C. L. = 20/20)	+	..	..	Slight haze	Severe late edema at 6 wk.; high astigmatism.	Cleared after 9 mo.; wears corneal lens 8 hr. a day
23	G. M.	M	26	Keratoconus	..	C. F. at 6 in. (C. L. = 20/100)	.....	..	..	+	Clear; sl. edema	Death from pulmonary embolus 3 wk. postoperative	Embolus from deep branch R. iliac vein
24	J. M.	M	26	Keratoconus	1½	20/60 — 2.00 ⌒ — 1.00 x 105	20/20 — 0.50 ⌒ + 2.50 x 95	+	..	..	Clear	Mild late edema at 10 wk.	Improved after 2 days of topical cortisone; recurrence in 4 mo.; cleared completely 5 mo.
25	M. O. R. E.	M	31	Keratoconus	2	20/400	20/60 —3.00 ⌒ + 7.00 x 100	+	..	..	Clear; sl. ectatic	.....	Extreme keratoconus
26	..... L. E.	..	..	Keratoconus	5	C. F. at 6 in.	20/30 — 4.00 cyl x 10	+	..	..	Clear	.....	Extreme keratoconus
27	L. R.	M	29	Keratoconus	4	3/200	20/20 + 0.50 ⌒ — 5.00 x 165	+	..	..	Clear	Two small iris adhesions to wound; secondary glaucoma	Adhesions separated 18 days; postoperative glaucoma controlled by cyclodialysis 2 mo. postoperative
28	J. S.	F	51	Keratoconus	5	3/200 — 8.00 sph	20/40 — 11.50 ⌒ — 1.50 x 90	+	..	..	Clear	.....	Severe hypertensive C. V. disease
29	E. S.	M	46	Keratoconus	3	2/200	20/25 — 10.00 sph	+	..	..	Clear; ectatic	Severe blepharospasm; slight displacement of graft 1st postoperative day	.....
30	P. S. R. E.	F	17	Keratoconus	1¼	20/300 — 9.50 sph	20/20 + 2.50 cyl x 40	+	..	..	Clear	Late edema at 3 mo.	Cleared in 3 days with cortisone drops; continued 6 mo.
31	..... L. E.	..	..	Keratoconus	2	20/400 — 9.50 sph	20/25 — 1.50 ⌒ + 3.00 x 112	+	..	..	Clear	.....	.....
32	M. W.	F	20	Keratoconus	5	20/300	20/20 — 9.50 ⌒ — 3.00 x 165	+	..	..	Clear	Fine iris adhesions at nasal corners of graft	Adhesions freed with spatula 1 mo. postoperative
33	H. Y.	M	31	Keratoconus	2	20/400	20/30 — 4.00 ⌒ — 2.50 x 20	+	..	..	Clear	Late edema at 13 mo.; graft perfectly transparent before	Cleared in 5 days, topical cortisone; recurrence 5 days after cessation; treatment resumed
34	J. C. R. E.	M	23	Keratoconus	2	20/800	20/20 — 2.00 ⌒ — 4.50 x 25	+	..	..	Clear	.....	.....

TABLE 6.—*Summary of Case Histories**—Continued

Case No.	Patient	Sex	Age, Yr.	Diagnosis	Follow-Up, Yr.	Vision and Refraction		Visual Result			Final State of Graft	Complications	Comment †
						Preoperative	Postoperative	Improved	Not Improved	Worse			
							Primary Transplants						
35	..... L. E.	..	..	Keratoconus	2	20/800	20/50 − 1.50 ⊃ − 4.00 x 60	+	..	..	Slightly hazy	Late edema at 3 mo.	Cortisone topically for 6 mo.; slight opacity remained
36	G. L. B.	M	23	Keratoconus	7	20/800	20/25 + 2.50 cyl x 45	+	..	..	Clear	Small iris adhesion freed with spatula 1 mo. postoperative	.....
37	D. M.	F	24	Keratoconus	1½	20/200	20/30 Without correction	+	..	..	Clear	.....	.....
38	C. J. F.	M	31	Interstitial keratitis; vascular nebulas	7	5/200	20/80	+	..	..	Faintly nebulous	Small iris adhesion freed 1 mo. postoperative	.....
39	S. M.	F	14	Interstitial keratitis; diffuse nebula, deep vessels	5	20/800	20/400 − 3.00 ⊃ − 5.00 x 45	..	+	..	Clear	Disseminated choroiditis of congenital syphilis	Amblyopia
40	J. McD.	F	54	Interstitial keratitis; diffuse nebula; few vessels	..	C. F. at 1 in.	.....	..	..	+	.....	Expulsive choroidal hemorrhage following operation	Delirium from scopolamine
41	N. B. M. (LAH)	F	47	Interstitial keratitis; central nebulas	6	20/200 − 2.50 cyl x 30	20/30 + 2.25 ⊃ + 2.75 x 135	+	..	..	Clear	.....	.....
42	R. M.	F	43	Interstitial keratitis; band-form keratopathy; cataract	4	L. P.	C. F. at 2 ft.	+	..	..	Nebulous, avascular	Vascularization of graft periphery; uveitis from hypermature cataract	1,100 r x-rays postoperative; cataract extraction 6 mo. after graft
43	W. P.	M	37	Interstitial keratitis; central leucoma	5	3/200	20/40 − 2.00 ⊃ − 2.00 x 80	+	..	..	Periphery nebulous	.....	.....
44	M. R.	F	31	Interstitial keratitis; ectasia of cornea	6	C. F. at 6 in. − 20.00 sph	20/200 − 20.00 sph	+	..	..	Nebulous	Iris adhesions extensive; lens also in contact with cornea and iris above	Adhesions separated 4 mo. postoperative; lens clear; tension normal
45	D. P. R. E.	F	20	Interstitial keratitis; central leucoma	2	C. F. at 2 ft.	20/400	+	..	..	Clear	.....	Amblyopia
46	..... L. E.	..	..	Interstitial keratitis; central leucoma	1½	20/70 + 0.50 ⊃ + 3.00 x 70	20/50 − 2.50 cyl x 5	+	..	..	Clear	Graft ectatic in upper half, where cornea very thin	Ectatic border cut and resutured 4 mo. postoperative
47	D. S. (LAH)	F	26	Interstitial keratitis; central nebula; ectasia	6	C. F. at 6 in.	20/50	+	..	..	Clear	Delayed restoration anterior chamber; glaucoma; edema of graft 4 wk.	Glaucoma subsided with miotics; graft cleared in 8 mo.
48	J. S.	M	45	Interstitial keratitis; central calcareous leucoma	8	20/300 − 14.00 sph	20/100 − 14.00 sph (C. L. = 20/50)	+	..	..	Clear; slightly ectatic	Secondary glaucoma aggravated by keratoplasty	Cyclodialysis 1 yr. after keratoplasty controlled glaucoma
49	F. C. (SUH)	F	19	Interstitial keratitis; vascular nebulas	15	15/200	20/30 − 13.00 ⊃ − 2.50 x 15	+	..	..	Clear; mod. ectatic	Myopia increase over 5 yr. period	.....
50	D. P.	M	44	Interstitial keratitis; central leucoma; vascular	8	20/400	20/400	..	+	..	Nebulous; slightly vascular	Extensive iris adhesion freed by iridectomy; mod. vascularization	.....

51	F. G.	F	53	Interstitial keratitis; diffuse nebulas	1⅛	20/800 — 4.25 ⊂ + 3.25 x 65	20/30 — 4.00 cyl x 180	+	..	..	Clear	.....	.....
52	R. A.	M	27	Adherent leucoma (total) after perforating ulcer	1½	H. M.	20/70 — 1.50 ⊂ — 2.50 x 5	+	..	..	Nebulous	Hemorrhage into anterior chamber 5th day; late edema at 5 wk.	Edema subsided in 10 mo.; topical hydrocortisone; cosmetic result good
53	D. B.	M	40	Central leucoma; perforating ulcer	13	H. M.	H. M.	..	+	..	Clear	.....	Vitreous cloudy; amblyopia
54	M. G. (SUH)	M	38	Vascular leucoma after keratitis, superficial, at age 3	7	C. F. at 1 ft.	1/200	..	+	..	Nebulous, partly vascular	Iris adhesion freed 3 mo. after keratoplasty; late edema at 1 mo.	Edema persisted
55	A. G. (VAH)	M	30	Dense vascular leucoma; aphakia; occluded pupil	1½	L. P.	H. M.	..	+	..	Nebulous	Small iris adhesion, separated through cyclodialysis 6 mo. postoperative	Iridotomy to be done
56	R. G.	M	41	Central leucoma with descemetocele after ulcer	7	2/200	20/70 — 10.00 ⊂ — 6.00 x 12	+	..	..	Clear	Fine iris adhesion broke spontaneously	600 r contact x-rays postoperative
57	R. H. (VAH)	M	25	Extremely malignant exophthalmos; dense nebula with ectasia	1½	C. F. at 1 ft.	20/200	..	+	..	Nebulous in lower 2/3	Difficult to protect lower half of cornea; chronic conjunctivitis	Hemolytic Staph. aureus; insensitive to all antibiotics; sensitive to sulfathiazole
58	T. S. J.	M	38	Central opacity after ulcer	13	C. F. at 5 ft.	20/200 — 5.00 cyl x 180	+	..	..	Clear; slightly ectatic	Fine iris adhesion	.....
59	W. M.	M	..	Adherent leucoma; perforated ulcer	1⅛	C. F. at 5 ft.	20/40 — 1.50 sph	+	..	..	Faintly nebulous	Small iris adhesion freed 2 mo. postoperative	Adhesions also freed prior to transplant
60	R. P.	M	58	Vascular leucoma after severe herpetic keratitis	13	C. F. at 2 ft.	C. F. at 3 ft.	..	+	..	Cloudy	Recipient cornea thick, vascular	.....
61	T. O. (VAH)	M	44	Central leucoma after infection	2	H. M.	20/20 + 14.00 ⊂ + 1.00 x 180	+	..	..	Clear	Lens capsule injured by trephine; extracapsular extraction through trephine hole	Small cortical fragment absorbed without complication; cortisone
62	B. R.	F	55	Total leucoma aphakia; suppurative keratitis	2	L. P.	4/200	+	..	..	Clear 2 yr.; nebulous	Cornea thick; pupillary membrane excised at time of transplant	Graft done for temporary improvement
63	L. T.	M	20	Dense adherent leucoma; perforating ulcer	2	C. F. at 2 ft.	20/20 — 5.00 sph	+	..	..	Clear	Adhesions of iris freed at at time of transplant	.....
64	G. T.	M	46	Disciform keratitis; moderate vascularity	6	C. F. at 2 ft.	20/50 — 5.00 ⊂ — 3.00 x 60	+	..	..	Small central nebula	Late edema at 4 wk.; vessels in periphery	1,000 r, contact x-rays; cleared in 12 mo.
65	S. D. (LAH)	M	31	Disciform keratitis; central leucoma	8	H. M.	20/100	+	..	..	Faintly nebulous	Vessels in periphery 2 wk. postoperative	500 r contact x-rays
66	R. H.	F	29	Disciform keratitis; eccentric vascular leucoma	3	20/800	20/200	+	..	..	Central nebula, vascular	Recurrent late edema at 2 to 18 mo.	Cortisone preoperative and postoperative

TABLE 6.—*Summary of Case Histories**—Continued

Case No.	Patient	Sex	Age, Yr.	Diagnosis	Follow-Up, Yr.	Vision and Refraction		Visual Result			Final State of Graft	Complications	Comment †
						Preoperative	Postoperative	Improved	Not Improved	Worse			
							Primary Transplants						
67	L. I.	M	40	Disciform keratitis; eccentric vascular leucoma	5	20/800	20/30 + 4.00 ⌒ + 3.50 x 80	+	..	..	Faint central macula	Severe late edema at 6 wk.; F. B. in graft 9 mo. postoperative	Slow clearing of edema over 16 mo.; macula from F. B.
68	G. R. (SUH) R. E.	F	55	Phlyctenular keratitis; calcareous degeneration	14	3/200	20/40	+	..	..	Faint nebula	.....	.....
69	..... L. E.	..	..	Phlyctenular keratitis; vascular nebulas	13	4/200	20/40	+	..	..	Faintly hazy	.....	.....
70	M. J. G. R. E.	F	24	Phlyctenular keratitis; high myopia	6	20/400 − 16.00 ⌒ + 3.00 x 155	20/200 − 14.00 ⌒ − 3.00 x 165	..	+	..	Clear	.....	Myopic retinal degeneration
71	..... L. E.	..	..	Phlyctenular keratitis; high myopia	2	20/400 − 18.00 ⌒ + 3.50 x 180	20/60 − 15.00 ⌒ − 4.00 x 150	+	..	..	Clear	Late edema at 6 wk.; vascularization of one quadrant	Cleared in 6 mo. 500 r contact x-rays
72	A. R.	F	32	Phlyctenular keratitis; calcareous degeneration; high myopia	3	C. F. at 6 in.	20/200	+	..	..	One-half nebulous	Late edema at 1 mo.	Cleared in 2 yr.; topical cortisone; 600 r contact x-rays
73	J. S. L. (SUH)	M	58	Trachomatous keratitis	13	C. F. at 2 ft. + 5.50 ⌒ + 2.00 x 180	C. F. at 2 ft.	..	+	..	Nebulous	Small chronic fistula at one corner of graft	Fistula closed with conjunctival flap
74	C. K. (SUH)	M	..	Trachomatous keratitis	9	6/200	5/200	..	+	..	Nebulous	Chronic fistula closed spontaneously; iris adherent	.....
75	M. W.	M	50	T. B. keratitis; vascular leucoma	4	20/200 + 2.00 ⌒ + 0.75 x 90	20/25 − 3.00 ⌒ − 5.00 x 142	+	..	..	Clear	Mild late edema at 3 mo.	Cleared in 2 mo., local cortisone
76	L. D. R. E.	M	54	Groenouw's dystrophy	6	20/630	20/70 − 17.00 ⌒ − 3.00 x 120	+	..	..	Clear	.....	High myopia with retinal changes
77	..... L. E.	..	..	Groenouw's dystrophy	4	20/300	20/60 − 17.50 ⌒ − 2.50 x 90	+	..	..	Clear	.....	High myopia with retinal changes
78	E. S. (VAH) R. E.	M	38	Groenouw's dystrophy	3	20/400 + 0.50 ⌒ + 5.00 x 105	20/30 − 6.00 ⌒ − 2.00 x 180	+	..	..	Clear; slightly ectatic	.....	.....
79	..... L. E.	..	..	Groenouw's dystrophy	2	20/400 + 5.00 cyl x 110	20/30 − 1.00 ⌒ − 3.00 x 180	+	..	..	Clear	.....	.....
80	J. S. R. E.	M	48	Groenouw's dystrophy, severe	1½	H. M.	20/300 + 10.00 sph	+	..	..	Nebulous	Malignant glaucoma 48 hr. after keratoplasty (other eye had same complication)	Iridectomy; resutured graft; lens extraction
81	W. S.	M	20	Dystrophy, congenital, unclassified (lipid ?)	6	20/400	C. F. at 4 ft.	..	..	+	Cloudy	Chronic edema of graft; dystrophy invaded graft —2 mo.	Second transplant
82	B. W. (SUH)	F	29	Dystrophy, congenital, unclassified (lipid ?)	9	10/200	3/200	..	..	+	Opaque	Dystrophy involved graft after 1 mo.	Second transplant

83	R. B.	M	62	Fuchs dystrophy; mature cataract	1½	L. P.	20/60 + 10.00 sph	+	..	..	Clear; fine folds in Descemet's	.....	Cataract removed 8 mo. postoperative; scleral incision
84	C. B. W.	M	55	Fuchs dystrophy; aphakia; pitting edema of cornea	3	L. P.	C. F. at 3 ft.	+	..	..	Total keratoplasty; nebulous	Vascularization of periphery	Dystrophy caused by damage to endothelium at cataract operation
85	G. D.	M	50	Dynamite injury; aphakia; aniridia	3	H. M.	C. F. at 3 ft. + 16.00 sph	+	..	..	Nebulous	Secondary glaucoma aggravated by keratoplasty	Glaucoma controlled by cyclodialysis 3 mo. postoperative
86	A. M.	M	51	Dynamite injury; leucoma; lens opacities	6	C. F. at 2 ft.	C. F. at 4 ft.	..	+	..	Partly nebulous; vascular	Cornea very thin from previous lamellar keratectomy	1,000 r contact x-rays; central scotoma
87	L. V.	M	..	Grenade injury; opacity with foreign bodies; cataract	7	20/200	20/80 — 1.00 ⊃ — 1.00 x 95	+	..	..	Clear	.....	Progression of cataract
88	W. McG.	M	50	Blast injury; vascular leucoma	7	L. P.	20/400	+	..	..	Nebulous; mod. vascular	.....	.....
89	W. P. (VAH)	M	35	Lye burn; vascular leucoma	2	L. P.	L. P.	..	+	..	Opaque	Early vascularization and opacification; poor union	Preoperative beta irradiation; peritomy with superficial keratectomy; second transplant
90	H. L. B.	M	45	Hydrochloric; acid burn; vascular leucoma; secondary glaucoma	15	H. M.	5/200	..	+	..	Clear	Secondary glaucoma aggravated by graft	Preliminary iridectomy; cyclodialysis 3 wk. after graft controlled glaucoma; central scotoma
91	W. C.	M	25	Chromic and sulfuric acid burn; total leucoma and symblepharon	2	L. P.	L. P.	..	+	..	Opaque	Delayed union of graft; rapid vascularization	Preliminary mucous membrane graft and keratectomy; second transplant
92	E. D. F. (VAH)	M	21	Leucoma—coral sand in cornea	8	10/200	20/15 — 3.00 cyl x 120	+	..	..	Clear	.....	.....
93	A. H.	M	39	Perforating injury; adherent leucoma; aphakia	1½	H. M.	20/200 + 13.00 ⊃ + 2.50 x 125	+	..	..	Partly nebulous	Membrane on vitreous face with round central opening	Vitreous aspirated before keratoplasty to avoid prolapse
							Secondary Transplants						
94	V. G. (VAH)	M	26	Keratoconus; transplant opaque; iris adherent	8	H. M.	L. P.	..	..	+	Opaque vascular	Iridectomy for secondary glaucoma	Third transplant (See Case 95)
95	V. G. (VAH)	M	26	Secondary graft opaque; 3d transplant	8	L. P.	No. L. P.	..	..	+	Opaque vascular	Severe secondary glaucoma	See Case 94
96	D. P.	M	44	Interstitial keratitis; graft nebulous	8	20/400	20/400 C. L. = 20/60	..	+	..	Faintly nebulous	.....	See Case 50 Wears contact lens at work
97	A. P. (VAH)	M	35	Lye burn	2	L. P.	L. P.	..	+	..	Opaque	Small fistula closed with buccal mucous membrane	See Case 89
98	B. L. W. (SUH)	F	29	Dystrophy involving graft	9	3/200	1/200	..	..	+	Opaque	Retrocorneal membrane; recurrence dystrophy	See Case 82
99	W. S.	M	20	Dystrophy invading graft	6	C. F. at 4 ft.	C. F. at 2 ft.	..	..	+	Cloudy	Recurrence of dystrophy in graft after 3 wk.	See Case 81 Systemic cortisone
100	W. C.	M	25	Acid burn; opaque graft	2	L. P.	L. P.	..	..	+	Opaque	Small fistula closed spontaneously	See Case 91

* VAH indicates Veterans Hospital, San Francisco; LAH, Letterman Army Hospital, San Francisco; SUH, Stanford University Hospital, San Francisco; C. L., vision with contact lens, if lens was worn satisfactorily. When refraction is not recorded, vision could not be improved with glasses.

† Numbers refer to case numbers. Case details described in the text have in many instances been omitted for brevity.

able minute, fairly uniform, whitish dots, which involved all the layers of the stroma. Bowman's membrane and the epithelium appeared quite normal. The gross appearance of the corneas was suggestive of the opacity observed in Hurler's syndrome, and referred to in the past as "lipid dystrophy." The clinical course in the two cases was identical. The corneas were found to be slightly thicker than normal at the time of operation. There were no operative complications, and the grafts remained clear, with marked improvement in vision, for about two months. At the end of this time there appeared a progressive opacification of the transplants which resembled very closely the opacity in the surrounding cornea. There was slight edema, but no vascularization or inflammation. In both cases the first opaque graft was excised, and a second transplantation was performed. These secondary transplants became opacified in the same manner as the first transplants.

The case listed as one of "partial extrusion with opacification" has already been described under the discussion of the results in keratoconus.

One eye was lost through an expulsive choroidal hemorrhage, which occurred about five hours after operation (Case 40). The patient was a 55-year-old woman with bilateral nebulas due to parenchymatous keratitis in childhood. Keratoplasty was performed with the patient under general anesthesia, and morphine and scopolamine were given as preoperative medication. After operation the patient was completely disoriented and delirious and made violent efforts to leave the hospital. The hemorrhage occurred during one of these episodes of exertion. This case and the case of death from pulmonary embolism are included in this review of the visual results of keratoplasty in order to present a complete picture of what may be expected in any good-sized series.

SUMMARY AND CONCLUSIONS

The visual results in a series of 100 consecutive partial penetrating keratoplasties, together with their complications, are reviewed. In the analysis of the results, no cases have been excluded for any reason whatsoever. With the exception of a case of expulsive hemorrhage and a case in which death occurred from pulmonary embolism, the minimal period of observation has been 18 months. The cases selected for operation were not chosen because of favorable prognosis; therefore, this series does not represent a specially selected one. Selection was made on the basis of the patient's need or desire for improvement in vision. Only those patients in which the prognosis was believed hopeless were denied operation. The preponderance of keratoconus cases in this series probably is representative of the distribution of the various types of corneal conditions which may require keratoplasty in the United States. In comparison with the series of cases reported by European authors, we have many fewer cases of suppurative keratitis, trachoma, phlyctenular keratitis, and parenchymatous keratitis and a correspondingly higher proportion of corneal degenerations.

The results may be summarized as follows:

1. Improvement in vision as estimated by an increase of two steps or more in the visual acuity scale was achieved in 74%. This number also includes 14 cases in which the final visual acuity was 20/200 or less but in which preoperative vision was so poor as to warrant their description as improved.

2. In 41% of operations the visual acuity was improved to 20/40 or better. Twenty-six of these 41 cases were of keratoconus.

3. In 19% the visual acuity was improved to a level between 20/50 and 20/100.

4. In the most favorable types of corneal disorders (keratoconus, mild interstitial keratitis, circumscribed leucomas after infection, Groenouw's dystrophy, and phlyctenular keratitis) the percentage of improvement in vision was approximately 90.

5. There was no improvement following keratoplasty in 16%.

6. Ten per cent of operations resulted in poorer vision. Half of these operations were

retransplantations. Only five eyes were worse after operation, including one in a case of death.

The results summarized above suggest that previous pessimistic reports concerning penetrating keratoplasty in the United States do not give a true picture of the possibilities and hazards of the operation. The technical ability and experience of the surgeon are of fundamental importance for the success of this operation.

While it is true that the operation is simple in principle, it is also true that a slight error in surgical technique, or a slight departure from precision, may be the difference between success and failure. The introduction of direct suturing for fixating the graft has improved the chances of success by decreasing such complications as iris adhesions, delayed formation of the anterior chamber, and poor coaptation of the wound edges. At the same time, it has increased the technical demands upon the surgeon. It is to be expected that with the wider adoption of direct sutures there will be further improvement in the results of penetrating keratoplasty. With the proper selection of cases, good surgical technique, and careful postoperative treatment, the results in corneal transplantation should equal those in retinal detachment surgery. The operative hazard does not appear to be significantly greater than the hazard in cataract extraction.

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TREATMENT OF HERPES ZOSTER OPHTHALMICUS WITH CORTISONE OR CORTICOTROPIN

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THIS PAPER presents observations on the treatment of herpes zoster ophthalmicus in 11 patients, all of whom had ocular involvement, by cortisone or corticotropin given systemically. Relief of pain was generally prompt. Striking improvement was usually noted in the ocular lesions. Final visual results were highly encouraging.

From 1937 to 1945, our results had been extremely discouraging in this type of disease. Partial or complete loss of vision, as a result of secondary glaucoma or corneal opacity, was not infrequent. In 1945, in view of the excellent results reported by Friedenwald [1] and Gundersen,* we began to employ immune serum therapeutically, with what seemed to be a more favorable outcome. In a group of patients, comparable in size to our present series, no impairment of vision resulted. The treatment of herpes zoster ophthalmicus with immune serum, however, involves certain difficulties. Frequent transfusions are necessary, necessitating a number of donors, who are often difficult to obtain. Furthermore, the hazards of serum reaction and infection are enhanced by the necessity for multiple transfusions.

Because of these disadvantages, other therapeutic approaches were utilized as they became available. A small number of patients were treated by antibiotics, including chlortetracycline (Aureomycin) and chloramphenicol, but no influence on the course of the disease was observed.

When corticotropin and cortisone were introduced for systemic therapy in ophthalmology, we first employed these substances as an adjunct to immune serum and, with greater experience in their use, finally omitted the use of immune serum entirely. A review of the available literature † revealed that 24 patients with herpes zoster had been treated with systemic cortisone or corticotropine. Fifteen of these patients had herpes zoster ophthalmicus with ocular involvement (Table 1). This treatment resulted in prompt relief of pain and usually striking improvement in the ocular lesion. Thirteen of the reported patients recovered completely after a short duration; 1 improved after three months, and 1 relapsed. It was concluded from this review, as pointed out by Duke-Elder,[4] that systemic cortisone or corticotropin is indicated in treatment of herpes zoster ophthalmicus. The results obtained in the treatment of the following 11 patients (Table 2) tend to corroborate this conclusion.

REPORT OF CASES

CASE 1.—W. H., a 46-year-old white man, was admitted to the neurosurgical service of the Hospital of the University of Pennsylvania on April 21, 1951, for observation because of severe left frontal pain and a history of having injured his head in a fall four weeks previously. One day before admission he developed a rash over the left frontal region.

Neurological examination was negative.

Routine laboratory studies, including a chest x-ray, were normal.

Ophthalmologic Study.—On April 22, an ophthalmologic consultation revealed the following:

Visual Acuity (corrected): O. D. 6/5
O. S. 6/12

Ocular Tension: 18 mm. Hg (Schiøtz) in each eye.

External examination: Herpetic vesicles of the skin were seen over the ophthalmic division of the left trigeminal nerve and the left side of the nose. The conjunctiva of the left eye was injected.

Slit-Lamp Examination: Findings were normal except for the conjunctival hyperemia of the left eye.

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* References 2 and 3.

† References 5 through 10.

Ophthalmoscopic Examination: Both fundi were normal.

Course.—On April 26, 1951, the patient was transferred to the ophthalmology service because a faint aqueous flare, and floaters were noted in conjunction with a localized superficial corneal infiltrate temporally. Treatment was started with local cortisone and atropine. On April 28, intravenous administration of 25 mg. of corticotropin daily was instituted and continued for five days. Relief of pain occurred within two days. He was discharged on May 3. The keratitis, which involved the anterior layer of the stroma, remained active, but the symptoms were well controlled by cortisone instilled locally. The edge of the infiltrate was typically scalloped and was deeper on the advancing border, which extended toward the pupillary border. Signs of mild activity recurred intermittently until Sept. 11, 1952. Since that time the eye has remained uninflamed. The vision is 6/6.

CASE 2.—R. O., a 41-year-old white man, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on April 17, 1952. He gave a history of severe pain accompanied by a vesicular eruption of the skin over the distribution of the ophthalmic division of the left fifth nerve of three weeks' duration.

Findings on Admission

Visual Acuity (corrected): O. D. 6/6
O. S. 6/20

Ocular Tension: O. D. 20 mm. Hg (Schiøtz)
O. S. 29 mm. Hg (Schiøtz)

External Examination.—Herpetic vesicles were seen on the skin over the ophthalmic division of the left fifth nerve and the tip of the nose. The lids of the left eye were edematous. Circumcorneal injection was present. The left pupil was semidilated and did not react to light. There was a localized corneal opacity involving the anterior stroma of the left cornea within the limbus at about 2:00 o'clock.

Slit-Lamp Examination: The anterior segment of the right eye was normal. The left cornea was edematous in the upper temporal quadrant, with

TABLE 1.—*Treatment of Herpes Zoster Ophthalmicus by Systemic Use of Corticotropin or Cortisone*

Author	Year	No. of Patients	Results
Duke-Elder [4]	1951	4	Improvement
Olson and others [5]	1951	1	Complete remission
Leopold and others [6]	1951	2	Improvement, 1; relapse, 1
Nickel [7]	1951	1	Improvement
Arruga [8]	1951	1	Subjective improvement, but ocular involvement persisted 3 mo.
Poulin [9]	1952	4	Improvement
Gelfand [10]	1954	2	Rapid improvement, 1; slow improvement, 1
	Total	15	Improvement, 13; relapse, 1; improvement after 3 mo., 1

TABLE 2.—*Summary of Results in Treatment of Eleven Patients with Herpes Zoster Ophthalmicus by Cortisone or Corticotropin*

Patient, No.	Pain	Ocular Tension	Uveitis	Corneal Lesion
1. (W. H.)	Subsided in 2 days	Normal	Subsided promptly	Subsided, leaving scar in cornea after 16 mo.
2. (R. O.)	Subsided in 2 days	Normal in 2 days	Subsided in 2 days	Cleared in 8 mo.
3. (F. S.)	Persisted	Normal in 24 hr.	Subsided in 6 wk.	Cleared in 6 wk.
4. (R. O'N.)	Subsided promptly	Normal	Subsided in 6 wk.	Cleared in 2 wk.
5. (F. T.)	Subsided promptly	Normal in 2 days	Subsided in 5 days	Cleared in 5 days
6. (F. C.)	Subsided promptly	Normal after 3 days during recurrence	Subsided promptly; recurred after 4 mo. but cleared in 30 days	Cleared promptly
7. (V. P.)	Subsided in 24 hr.	Normal after 24 hr.	Subsided promptly; recurred but responded to local therapy	Cleared in 2 wk.
8. (C. B.)	Subsided in 24 hr.	Normal	Subsided gradually	Cleared promptly
9. (E. B.)	Subsided in 24 hr.	Normal	Subsided promptly	Cleared promptly
10. (M. D.)	Subsided in 2 days	Persisted; surgical intervention necessary	Persisted	Cleared in 2 days
11. (F. W.)	Subsided in 2 days	Normal	Subsided after 1 mo.	Not involved

infiltration of the stroma and folds in Descemet's membrane. An aqueous flare and floaters were noted.

Ophthalmoscopic Examination: Both fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On his admission to the hospital, cortisone and atropine were prescribed for local use. The following day corticotropin therapy with 20 mg. intravenously was started and continued for three days. On this regime the intraocular pressure fell to 19 mm. Hg, and the corneal opacity began to clear. Pain disappeared in 48 hours.

On April 20, cortisone was substituted for corticotropine. The intravenous administration was continued for 17 days, in combination with local use of the drug. The patient had no serious difficulty after discontinuing systemic cortisone, although the keratitis required eight months to subside. Recurrent photophobia and irritation, which were associated with the corneal lesion, were readily controlled by cortisone drops. His final visual acuity in the left eye was 6/6.

Case 3.—F. S., a 71-year-old white man, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on May 3, 1952, because of severe pain and the characteristic lesions of herpes zoster involving the maxillary and ophthalmic divisions of the right trigeminal nerve, of five days' duration.

Findings on Admission

Visual Acuity (corrected): O. D. 6/12
O. S. 6/12

Ocular Tension: 22 mm. Hg (Schiøtz) bilaterally.

External Examination: The upper and lower lids of the right eye were edematous. Marked conjunctival injection was present. The right corneal reflex was absent. The left eye was healthy.

Slit-Lamp Examination: Both anterior segments were normal.

Ophthalmoscopic Examination: The fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On May 9, six days after admission, signs of iritis developed. The ocular tension was 30 to 35 mm. Hg (Schiøtz) in the right eye. Systemic cortisone therapy was started, in a dosage of 300 mg. on the first day, 200 mg. on the second day, and 100 mg. daily thereafter. The pressure became normal in 24 hours. Despite this therapy, on May 16 the patient still had severe pain; he therefore was transferred to the neurosurgical service, at the suggestion of the Neurosurgical Department, where he underwent a subtotal avulsion of the right sensory root on May 26. The pain was greatly relieved, although some burning discomfort persisted. Cortisone therapy was discontinued because the eye became white and the aqueous had cleared remarkably.

The patient was discharged from the hospital on June 1, using atropine sulfate 1% and local cortisone drops. On June 4, exposure keratitis was noted, which required a tarsorrhapy. All treatment was discontinued on June 27.

Follow-up examination on Dec. 5, 1952, and June 9, 1954, revealed marked hypalgesia overlying the first division of the fifth nerve and complete anesthesia of the second division, with good visual function.

Case 4.—R. O'N., a 34-year-old white man, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on Oct. 21, 1952, because of herpes zoster ophthalmicus on the right, accompanied by severe pain of eight days' duration. The right eye had been painful, red, and sensitive to light for five days.

Findings on Admission

Visual Acuity (corrected): O. D. 6/30
O. S. 6/5
(pinhole) O. D. 6/12

Ocular Tension: 12 mm. Hg (Schiøtz) bilaterally.

External Examination: The lids of the right eye were edematous. Circumcorneal injection and diffuse corneal haze were present. The right pupil was smaller than the left and irregular in outline; it reacted sluggishly to light. The left eye was normal.

Slit-Lamp Examination: The right cornea was edematous and showed many folds in Descemet's membrane. Many keratic precipitates, a moderate to heavy aqueous flare, and many floaters were present. Posterior synechiae had formed from 6 to 10 o'clock inferotemporally. The iris was engorged and edematous.

Ophthalmoscopic Examination: The media of the right eye was hazy, but the disc and fundus were normal. The disc and fundus of the left eye were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—Systemic cortisone therapy of 100 mg. daily was instituted on admission to the hospital. Subconjunctival injections of epinephrine, atropine, and cocaine were given to the right eye to free the posterior synechiae. The keratitis and iritis subsided during the next two weeks, and the patient was discharged from the hospital on Nov. 5, although still receiving cortisone systemically. By Dec. 10 the eye was white and quiet, and all treatment was discontinued.

Case 5.—F. T., a 53-year-old white man, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on Oct. 25, 1952, because of typical right herpes zoster oph-

thalmicus of two weeks' duration. The right eye had been red and painful for one week. He had received systemic chlortetracycline (Aureomycin) and atropine drops in the right eye prior to admission.

Findings on Admission

Visual Acuity (corrected): O. D. 6/9
O. S. 6/6

Ocular Tension: O. D. 27 mm. Hg (Schiøtz)
O. S. 17 mm. Hg (Schiøtz)

External Examination: A vesicular eruption of the skin over the ophthalmic and maxillary divisions of the right trigeminal nerve was present. Circumcorneal injection and a hazy cornea of the right eye were obvious.

Slit-Lamp Examination: The right cornea showed diffuse edema with folds in Descemet's membrane. Many fine keratic precipitates, a moderately heavy aqueous flare, and many aqueous floaters were present.

Ophthalmoscopic Examination: The right media was hazy, due to corneal edema. Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission intravenous administration of corticotropin, 20 mg. daily, was instituted, as well as local use of atropine and cortisone. On this regime the corneal edema and the flare and floaters gradually subsided. Pain was promptly relived.

On Oct. 30, cortisone, 100 mg. daily, was substituted for the corticotropin, and he was discharged from the hospital, to be followed as an outpatient. The eye became entirely quiet, and on Nov. 19, systemic cortisone was discontinued. On Jan. 14, 1953, local treatment was discontinued. The final visual acuity in the right eye was 6/6 corrected.

Case 6.—F. C., a 43-year-old white woman, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on Jan. 5, 1953, because of right herpes zoster ophthalmicus and pain, of five days' duration. The right eye had been photophobic and red, and the vision had been blurred.

Findings on Admission

Visual Acuity (corrected): O. D. 6/7+
O. S. 6/6

Ocular Tension: O. D. 26 mm. Hg (Schiøtz)
O. S. 27 mm. Hg (Schiøtz)

External Examination: Moderate edema of the right upper and lower lids and herpetic vesicles over the ophthalmic division of the right fifth cranial nerve were noted. Chemosis of the conjunctiva of the right eye was present.

Slit-Lamp Examination: Superficial infiltrates at the lower limbus of the right cornea, keratic precipitates, a faint flare with a moderate number of floaters, and a slightly thickened iris were noted.

Ophthalmoscopic Examination: The media in the right eye were hazy, due to the corneal lesions. Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission, cortisone, 100 mg., was given and the dose repeated daily, in addition to local use of cortisone and atropine. The symptoms began to clear within 24 hours, and in one week the patient was discharged from the hospital. Slight atrophy of the temporal third of the iris stroma occurred. Systemic cortisone was discontinued on March 7. Signs of iridocyclitis recurred intermittently after this date. On April 11, 1953, a faint flare and a few keratic precipitates were noted, which subsided during the next four weeks of treatment with cortisone and atropine given locally. It recurred, and on June 13 the ocular tension was 40 mm. Hg (Schiøtz). It remained elevated, and systemic cortisone was reinstituted on June 30. The iridocyclitis became much severer, with many pigmented keratic precipitates. The inflammation gradually subsided, until by Aug. 31, 1953, inflammatory signs had largely subsided and the ocular tension was 17 mm. Hg (Schiøtz). Treatment was then discontinued. The final visual acuity was 6/6.

Case 7.—V. P., a 59-year-old white woman, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on March 15, 1953, because of right herpes zoster ophthalmicus of six days' duration, accompanied by severe pain. On the day of admission, the patient developed pain in her right eye with dimution of vision.

Findings on Admission

Visual Acuity (uncorrected): O. D. 6/100
O. S. 6/22

Visual Acuity (corrected): O. D. 6/60
O. S. 6/7.5

Ocular Tension: O. D. 40 mm. Hg (Schiøtz)
O. S. 19 mm. Hg (Schiøtz)

External Examination: Many vesicles were present over the ophthalmic division of the right fifth nerve and on the tip of the nose, with extensive edema of the right eyelids and chemosis of the conjunctiva. The pupil of the right eye was irregularly dilated to 5 mm. and did not react to light or in accommodation. Corneal sensitivity of the right eye was diminished.

Slit-Lamp Examination: Corneal edema with superficial infiltrate, many folds in Descemet's membrane, and a moderately heavy aqueous flare and floaters were noted in the right eye.

Gonioscopic Examination: Open angles were found in each eye.

Ophthalmoscopic Examination: Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission, local treatment with cortisone, chlorotetracycline, and atropine was instituted. Intravenous corticotropin, 20 mg. daily, was given, together with Crysticillin (penicillin G procaine) in aqueous suspension, 400,000 units, and streptomycin, 0.5 gm., intramuscularly twice daily. The pain subsided, and the intraocular pressure became normal the day after admission.

Corticotropin therapy was discontinued on April 2, and the patient was discharged on April 3, still using atropine and cortisone locally. The corneal infiltrate gradually cleared. On June 9, the eye became white and quiet, and several areas of atrophy of the iris stroma were noted. The ocular tension was 20 mm. Hg (Schiøtz) in each eye. Treatment was discontinued.

On June 30, 1953, there was a recurrence of the iridocyclitis. Local use of atropine and cortisone was reinstituted. Ocular pressure (Schiøtz) remained normal. The visual acuity of the right eye had returned by this time to 6/9+ corrected. An indolent, somewhat recurrent, iridocyclitis continued for nearly a year. The last signs of iridocyclitis were seen in April, 1954. Each recurrence has promptly disappeared with the administration of atropine and cortisone locally. On June 11, 1954, the eye was symptom-free and the vision 6/9 corrected.

Case 8.—C. B., a 48-year-old Negro man, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on May 11, 1953, because of left herpes zoster ophthalmicus, of nine days' duration, accompanied by severe pain. Six days before admission blurring of vision had occurred.

Findings on Admission

Visual Acuity (corrected): O. D. 6/6
O. S. 6/6

Ocular Tension: 20 mm. Hg (Schiøtz) bilaterally.

External Examination: Vesicles over the ophthalmic division of the left trigeminal nerve and tip of the nose were noted.

Slit-Lamp Examination: Subepithelial infiltrates were seen inferiorly in the left cornea. Many small keratic precipitates, an aqueous flare, and floaters were present.

Ophthalmoscopic Examination: Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were negative.

Course.—On admission, local treatment with atropine, cortisone, and penicillin and streptomycin solutions was started. Corticotropin, 20 mg., was administered intravenously and the injection repeated daily. The pain disappeared within 24 hours; the iridocyclitis improved rapidly, and on May 15 systemic corticotropin was discontinued. The patient was dischraged to the Ophthalmology Clinic on May 16, using cortisone and atropine locally. On June 12, it was noted that the cornea was entirely clear, but a faint flare persisted; local therapy therefore was continued. By Aug. 27, 1953, the eye was quiet and treatment was discontinued.

Case 9.—E. B., a 70-year-old white woman, was admitted to the ophthalmology service of the Hospital of the University of Pennsylvania on May 22, 1953, because of left herpes zoster ophthalmicus of six days' duration.

Findings on Admission

Visual Acuity (corrected): O. D. 6/60
O. S. 6/9

Ocular Tension: 20 mm. Hg (Schiøtz) in both eyes.

External Examination: Marked edema of the left lids was present. Hyperemia of the left frontal area over the bridge of the nose and vesicle formation over the ophthalmic branch of the fifth cranial nerve were noted. Circumcorneal injection and chemosis of the conjunctiva of the left eye were present. The left pupil was miotic.

Slit-Lamp Examination: Small superficial infiltrates of the left cornea within the limbus at 2 and 9 o'clock, with many folds in Descemet's membrane, were present.

Ophthalmoscopic Examination: Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission, atropine, chloramphenicol, and cortisone were given locally. Systemically, she was treated with intravenous corticotropin, 40 mg. daily, and chlortetracycline, 250 mg. four times daily. The following day the pain subsided. On May 25, the edema, hyperemia, and vesicles subsided, and the cornea had cleared. The patient was discharged on May 27, using local atropine and cortisone. The flare and floaters gradually disappeared by June 19, 1953, at which time the eye was white and quiet. The visual acuity was 6/9+ with correction.

Case 10.—M. D., a 72-year-old Negro woman, was first seen in the Ophthalmology Clinic of the Hospital of the University of Pennsylvania on Jan. 5, 1954, because of left trigeminal herpes zoster ophthalmicus and severe pain of five days' duration. On the day of admission photophobia developed and the left eye became red.

Findings on Admission

Visual Acuity (uncorrected): O. D. 6/7.5
O. S. 6/12

Visual-Acuity (corrected): O. D. 6/6
O. S. 6/9

Ocular Tension: O. D. 20 mm. Hg (Schiøtz)
O. S. 40 mm. Hg (Schiøtz)

External Examination: The lids of the left eye were edematous. Vesicles were present over the ophthalmic division of the left trigeminal nerve. There was a circumcorneal injection of the left eye, and gross corneal edema with infiltration of the upper limbus was noted. The left pupil was miotic but reacted to light and in accommodation. Sensitivity of the left cornea was absent to a wisp of cotton.

Slit-Lamp Examination: The left cornea was edematous, and subepithelial infiltrates were noted at the upper limbus. Flare and floaters were present.

Ophthalmoscopic Exmaination: Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission, local treatment with hydrocortisone, 2.5% solution, and atropine was instituted, and cortisone 100 mg. was given daily by mouth. The infiltrates in the cornea and the pain disappeared after two days of treatment. The intraocular pressure, however, continued to be elevated, varying from 37 to 45 mm. Hg (Schiøtz). The flare and floaters persisted. Visual acuity remained 6/12, corrected, but repeated visual fields revealed a superior Bjerrum scotoma. Because of the elevated intraocular pressure and the visual field defect, the patient was started on treatment with acetazoleamine (Diamox), 250 mg. twice daily, on April 22, 1954. This did not affect the elevated pressure; so the dosage of acetazolemide was increased to 250 mg. four times daily, without lowering the intraocular pressure. Because of the persistent elevated intraocular pressure, together with the visual field loss, cyclodiathermy of the lower half of the globe was performed on May 12. This resulted in the immediate control of the intraocular pressure. One week following the operative procedure, the intraocular pressure measured 17 mm. Hg (Schiøtz). The cortisone therapy consequently was discontinued on May 14,, although local atropine and hydrocortisone were continued. The flare and floaters have gradually diminished. By June 11, the left eye was white and quiet, and visual acuity was 6/12 corrected, and ocular tension 20 mm. Hg (Schiøtz).

Case II.—F. W., a 56-year-old white man, was admitted to the ophthalmology service, Hospital of the University of Pennsylvania, on May 5, 1954, because of right herpes zoster ophthalmicus with severe pain of six days' duration. On the day of admission the right eye became red and photophobic.

Findings on Admission

Visual Acuity (corrected): O. D. 6/6
O. S. 6/6—

Ocular Tension: 20 mm. Hg (Schiøtz) in each eye.

External Examination: Herpetic vesicles were present over the ophthalmic division of the right fifth nerve. Moderate edema of the right upper lid and faint circumcorneal injection were noted.

Slit-Lamp Examination: The right cornea was normal, but faint flare and floaters were noted.

Ophthalmoscopic Examination: Both discs and fundi were normal.

Laboratory Studies: Routine studies, including a chest x-ray, were normal.

Course.—On admission corticotropin (Acthar Gel), 40 mg., was given intramuscularly, in addition to atropine and hydrocortisone, 2.5% solution, used locally. After two days of this treatment, the pain subsided, although the aqueous flare and floaters persisted. He was discharged on May 10, on the same medication, to be followed as an outpatient. On May 14 the intramuscular use of corticotropin was discontinued. On June 14, the eye was entirely quiet, and all medication was discontinued.

COMMENT

The results obtained in the treatment of 11 patients with herpes zoster ophthalmicus, all showing ocular involvement, have been described. All of the patients had shown the characteristic, rather severe pain of herpes zoster. All showed the classic signs of iridocyclitis, occurring alone or accompanied by keratitis. Some were complicated by secondary glaucoma. In all but one instance, relief of pain was dramatic, nearly always disappearing, as observed by Gelfand,[10] within 24 to 36 hours. Inflammatory ocular signs showed rather rapid marked improvement, although in several instances a rather protracted mild, but recurrent, course ensued. The symptoms of this protracted rather mild iritis or keratoiritis were usually readily controlled by atropine and cortisone administered locally. Elevated ocular tension likewise usually subsided promptly. In one instance operative intervention was necessitated. In no instance was permanent visual loss encountered.

Herpes zoster is an acute infectious disease of viral origin, which may run a course of from a few days to several months. It is characterized by severe neuralgic pains, which in our small series of patients seem to be rather dramatically relieved by cortisone or corticotropin given early in the course of the disease. The disease is usually benign unless ocular involvement occurs. The

commonest ocular manifestations consist of keratitis, iritis, corneal ulceration, secondary glaucoma, or optic neuritis. The two most serious complications which lead to visual loss are corneal opacity and secondary glaucoma.

Treatment in the past, always empiric in nature, has involved a multiplicity of approaches. Immune serum, suggested first by Friedenwald and developed much more extensively by Gundersen, seemed to offer a real therapeutic advance. In our own experience visual loss was greatly reduced. The difficulties of obtaining an adequate supply of immune serum, while not insurmountable, lead to considerable objection to its use. Antibiotic therapy is considered to be of no value.

An increasing number of reports suggest that hormonal therapy, consisting of cortisone or corticotropin, is of great value. Antibiotics, given simultaneously, diminish or prevent secondary infection. These hormones probably in some way block the response of tissues to the viral agent. In this way they suppress the ocular reaction and prevent serious complications ordinarily encountered with this condition. It is very unlikely that cortisone or corticotropin has any specific action against the virus of herpes zoster.

SUMMARY

Cortisone and corticotropin seem to have exerted a favorable influence on herpes zoster ophthalmicus in the 11 patients reported in this paper.

Relief of pain usually occurred in one to two days.

Therapy with these hormones suppressed signs of ocular inflammation, such as iritis and keratitis, but was not curative, as shown by the frequent recurrence of symptoms.

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LIPOCHONDRODYSTROPHY (GARGOYLISM)

Pathologic Findings in Five Eyes of Three Patients

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LIPOCHONDRODYSTROPHY is a familial metabolic disorder in which a macromolecular substance is stored in many tissues and in which the maturation of cartilage is defective. There may be corneal clouding, mental deficiency, partial deafness, reduced vision, hepatosplenomegaly, and cardiac hypertrophy. Involvement of the bone causes dwarfing, kyphosis, and arthrogryposis. The skull is usually enlarged and the nasal bridge depressed. There may be hypertelorism, prominent supraorbital ridges, and prognathism. The skin is coarse, the lips thick, the ears enlarged, and the tongue enlarged and protruding. The hair is coarse and often gray in color.

Dr. John Thompson, of the Royal Infirmary, Edinburgh, recognized the condition in 1900 and called it "Johnny McL.'s disease." In 1908 and 1913, he found the same abnormality in siblings of this patient, and in 1924, he reported the cases to the Edinburgh Pediatric Club.[1] Putnam and Pelkan [3] credit Berkhan [2] with recording the first case in 1908. Hunter,[4] in 1916, described the condition under the title "A Rare Disease in Two Brothers"; neither patient showed corneal involvement.

Hurler,[5] in 1919, described a 4-year-old boy demonstrating all features of the condition, and Pfaundler,[6] the following year, reported an infant presenting a similar clinical picture. Ellis, Sheldon, and Capon,[7] in 1936, proposed the term gargoylism because of the large head and grotesque appearance of the face so often present. Despite the semantic inaccuracy of the term, the name gargoylism is now almost universally used. Washington [8] introduced the term lipochondrodystrophy, which has been used to classify the disease in the *Quarterly Cumulative Index Medicus* since 1941.

A number of other terms have been proposed for the condition: chondro-osteodystrophy (Cockayne [9] and Ashby and associates [10]); *polydystrophie* (Bindschedler [12]); lipochondrodysplasia (Cordes and Hogan [13]); dysostosis enchondralis (Menger [14]); *dysostotische Idiote-Gargoylisme* (Hässler [15]); *osteo-chondrodystrophie* (Nissler [16]); *osteo-arthropathie* (Schmidt [17]; Stens), and dysostosis multiplex (Binswanger and Ullrich [19]).

The condition, while uncommon, is not rare. Reilly and Lindsay [20] have reported 16 cases. Jervis,[21] in 1950, reviewed 138 examples recorded in the world literature and added 10. Caffey [22] stated that in his experience with roentgenograms the condition was third in frequency of all generalized intrinsic skeletal dystrophies.

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During a period of 15 years he observed 10 cases of gargoylism, 43 of classic achondroplasia, 15 of osteogenesis imperfecta, and 9 of hereditary multiple cartilaginous exostoses.

The disease is widely distributed and has been reported in the Chinese (Engel [23]) and in the Negro (Hubeny and Delano [24]; Lahey and associates [25]). Cases have also been reported from Australia (Sear and Maddox [26]) and South Africa (Jackson [27]; McDonald and Opie [28]).

The condition is often familial. In Jervis' [21] survey of 85 families, 26 had two or more members affected, and 52% showed a familial incidence. It was concluded that gargoylism was determined by a monomeric autosomal recessive gene, thus confirming the findings of Halperin and Curtis (1942).[29]

Njå [30] described five cases without corneal opacities in a Norwegian family. He postulated that there was a special sex-linked recessive form in which the corneas were clear. Millman and Whittick [31] supported this view and reported four, and possibly five, cases of gargoylism without corneal involvement in which the males appeared to inherit the condition as a sex-linked recessive character.

Usually no signs are evident at birth, although Ashby, Stewart, and Watkin [10] described a patient having a deformed skull and a repulsive appearance at birth. The second and third patients reported here were recognized at birth by the father to bear a strong resemblance to a child who had died earlier, presumably with the disease. The external manifestations usually appear in early childhood and are preceded by normal development. Corneal clouding has been seen at birth, but usually does not develop until after the sixth month.

The children are usually dull and apathetic and appear younger than their age. They are late in walking, and slow both physically and mentally, and bilateral pyramidal signs with weakness and ataxia may come on at any stage. They are short in stature, and some are pronounced dwarfs. The head is large and misshapen, and the frontal and temporal ridges are prominent. The ears are large and set low on the skull. The bridge of the nose is wide and depressed, and breathing is noisy and often labored. The mouth is large; the lips are thick, and the teeth are widely spaced. The tongue is large and protuberant, as though too big for the mouth, and has transverse furrows. The mandible is massive.

The neck is short and broad, and the enlarged head appears to rest directly upon the thorax. The chest is wide and the spine distorted by a dorsolumbar kyphosis. The abdomen is protuberant, and umbilical and inguinal hernias are common. The liver and spleen are enlarged but do not account for the protuberant abdomen.

The flexion deformity of the extremities occurs in a high percentage of patients. This is characterized by pronounced limitation of extension, but no interference with flexion of the involved joints, and is most frequent in the fingers, causing a "claw hand." The flexion deformity may cause a crouching posture.

Hirsutism occurs in a large number of patients, and a nonspecific dermatitis has been described.

Roentgenographic examination demonstrates involvement of the entire skeleton. Enlargement of the head is associated with an elongated and shallow sella turcica. The scapulas and clavicles are widened, and the ribs are narrow at their vertebral insertions and broad in the blade.

The thoracic bodies of the vertebral column are distorted with kyphosis. There is a gross discrepancy in development between the pelvis, which is infantile, and the femurs, which are massive.

REPORT OF CASES

CASE I.—W. B., a 6-year-old white boy, was first seen at the University of Chicago Clinics on Jan. 5, 1940, because of retarded development. He was the eighth of nine children, the third and fourth of whom were girls, and, according to the mother, these girls had exactly the same appearance as the patient. The third child appeared abnormal about the fourth month and died at 7 years of age, of pneumonia. The fourth child died at 4 years of age, with pertussis. The mother stated that her great-great-grandfather was a dwarf, 46 in. (117 cm.) tall, and was intelligent, healthy, and normal in every way. His wife was 6 ft. (183 cm.) tall. Until the present children had been born, there were no developmental abnormalities in the family.

The patient was born at term after 12 hours of labor. He weighed 10 lb. (4,536 gm.). When he was only a few days old, the mother believed that the child looked like her two daughters who had died. His development was slow, and he did not walk until he was 3 years old. When he was 4 months old, there was redness of both eyes and a nasal discharge, and by 6 months of age the corneas were cloudy. His head had always seemed large, and as he grew older, the bridge of his nose became more depressed and the base broader. His tongue enlarged, and he was unable to make distinct sounds. His growth was retarded; his bones were deformed, with short and broad fingers and toes, and he had an unsteady gait. The abdomen was protuberant, and an umbilical hernia was present from 4 months of age.

When he was 6 years old, the head circumference was 54 cm. There was marked protrusion of the frontal bossae. The nose was obstructed by a thick, purulent discharge, and he breathed through his mouth. His lips were thick; the teeth were badly formed, and many dental caries were present. The tongue was thick and coated and projected through his teeth.

His neck was very short, and his head appeared to rest upon his shoulders. The heart was moderately enlarged, and there was a soft apical systolic murmur. The abdomen was 67 cm. in circumference. A marked kyphosis of the lower thoracic and the lumbar spine was present. His height was 81 cm., crown-navel measurement 72 cm., and navel-heel measurement 39 cm. The digits were short and stubby, but the joints were not notably involved.

The orbits measured 28 mm. vertically and 34 mm. horizontally. The right upper lid was slightly edematous, and there was moderate injection of the conjunctiva, with a purulent secretion in the canthi. This conjunctivitis responded quickly to treatment and was not significant. The interpupillary diameter was 52 mm. The Hertel exophthalmometer measurements were 16 mm. bilaterally. Each cornea measured 12 mm. vertically and horizontally. Tension with the Souter tonometer was 42 mm. Hg in the right eye and 22 mm. Hg in the left eye. Treatment with local instillation of pilocarpine did not affect the tension or the appearance of the cornea. Both corneas were hazy, and the infiltration seemed to be largely limited to the central stroma. The child was not examined under the slit lamp. The anterior chamber was deep in each eye, and the irises were brown. The pupils were 5 mm. in diameter and reacted poorly to light and in convergence. It was not possible to see details of the fundi through the clouded corneas.

The patient went home unchanged and was readmitted Feb. 3, 1942, with fever, dyspnea, and swelling of the ankles, feet, and abdomen. He died the following day, of bronchopneumonia, at the age of 8 years.

The hemogram revealed hemoglobin 15 gm. per 100 cc., erythrocytes 5,750,000; differential count was 56% polymorphonuclear leucocytes and 44% lymphocytes. Blood chemical studies revealed serum cholesterol 130 mg., serum calcium 13.8 mg., serum phosphorus 12.4 mg., and nonprotein nitrogen 26.7 mg., per 100 cc. The intravenous glucose tolerance test was normal.

Roentgenograms indicated infantile development of the pelvis, which showed no fusion of the ischium and pubis. The acetabulum components were separated from each other by cartilage. The femoral shafts had the texture and cortex of adult bone. The metacarpals and phalanges were broad and short. The radius and ulna were short and broad and their distal ends flared. The heart was slightly enlarged. The anteroposterior diameter of the skull was lengthened and the sella turcica grotesquely elongated.

The autopsy was performed by Dr. A. C. Hopps. The pathologic findings will be reported elsewhere; thus, only the major abnormalities will be presented here.

Fibrocaseous tuberculosis was present in the right lower lobe, and bronchopneumonia was present. The heart, liver, and spleen were markedly enlarged. Histologically, many muscle fibers of the heart showed waxy degeneration and actual fibrous tissue replacement of muscle in some areas. Staining with Sudan III indicated a diffuse fatty degeneration, but many intracellular vacuoles

Fig. 1 (Case 1).—W. B., aged 6 years, with his normal 8-year-old brother. Reproduced from Grulee, C. G., and Eley, R. C.: The Child in Health and Disease, Ed. 2, Baltimore, Williams & Wilkins Company, 1952, p. 793.

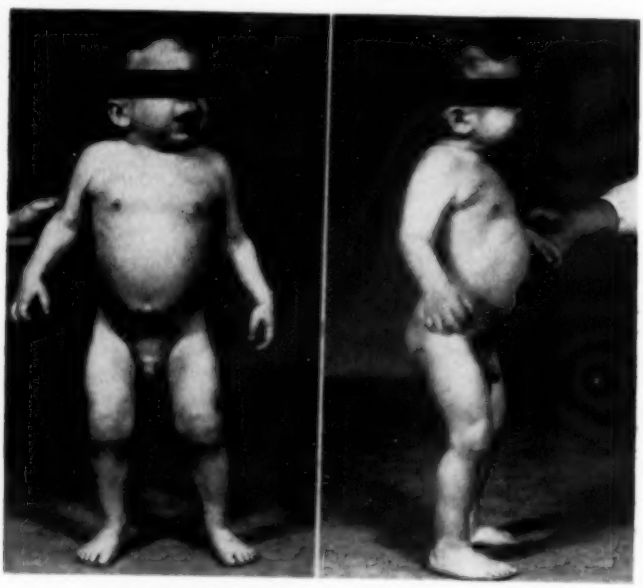

Fig. 2 (Case 2)—D. C., aged 4 years.

Fig. 3 (Case 3).—T. C., aged 1 year 7 months. Reproduced from Grulee, C. G., and Eley, R. C.: The Child in Health and Disease, Ed. 2, Baltimore, Williams & Wilkins Company, 1952, p. 794.

Fig. 4 (Case 1).—Roentgen-ray photograph of the skull. The sella turcica is elongated. There is diastasis of the coronal suture and erosion of the outer table in the occipital region.

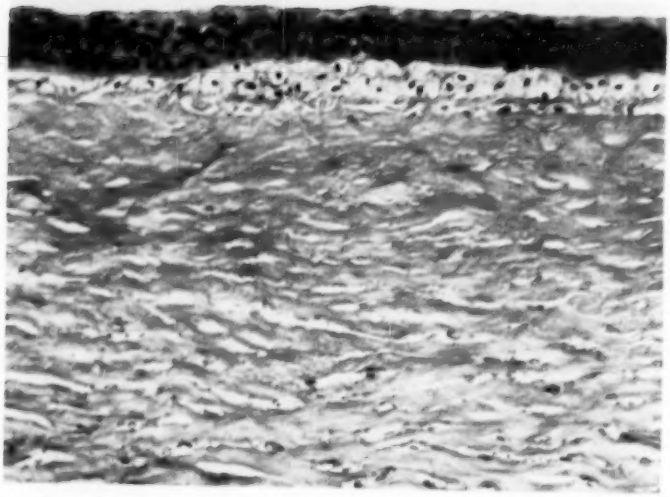

Fig. 5 (Case 2).—Vacuolation of the cells immediately beneath the corneal epithelium with separation of the corneal lamellae. Bowman's membrane has been almost entirely replaced with swollen cells. Aniline blue-orange G-fuchsin; reduced 2/5 from mag. × 250.

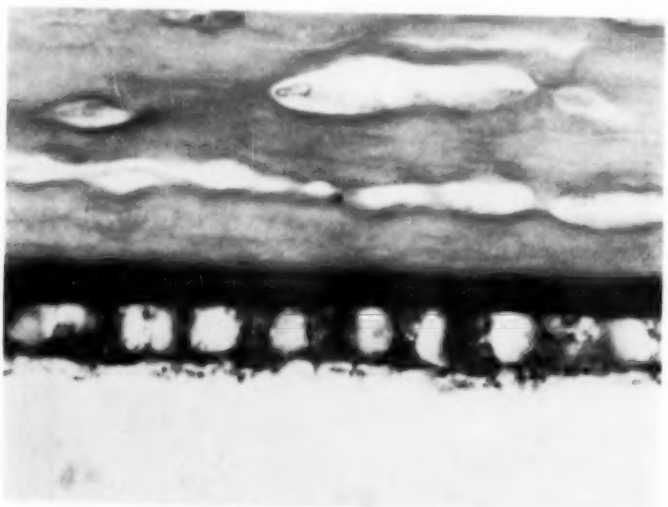

Fig. 6 (Case 1).—Markedly swollen corneal endothelium with normal Descemet's layer and abnormal stroma. Aniline blue-orange G-fuchsin; reduced 2/5 from mag. × 1,035.

did not stain. Practically every liver cell was vacuolated. The majority of cells were filled with smaller vacuoles, averaging 5 to 7 micra in diameter, and six to eight such vacuoles were seen in one cell in the plainest section. The spleen showed passive congestion. A symmetrical internal hydrocephalus was present, together with convolutional atrophy of both cerebral hemispheres and cerebellar atrophy.

Case 2.—The patient, D. C., was first seen on March 11, 1943, when he was 3 years old. He was the third of four children, the second, third, and fourth of whom were abnormal. The fourth sibling is the third case of this report. The father's parents were second cousins.

The patient's brother, the second sibling, died suddenly when 17 months old, apparently with internal hydrocephalus. He had never sat alone and was generally retarded. His head was enlarged, but the eyes were normal. The liver was palpable but did not appear to be enlarged. A right inguinal hernia was present, and there was flaccidity of all muscles. Autopsy was limited to his head, which showed an internal and external hydrocephalus. Many cells had a balloon-like appearance, which could not be definitely distinguished from that due to postmortem changes.

The present patient had an uneventful delivery and a birth weight of 8 lb. 8 oz. (3,856 gm.). His father felt that the child looked "unfinished" at birth, as had the earlier sibling, and suggested to his physician the possibility of a similar defect. Umbilical and inguinal hernias were present and were repaired when the child was 2 years old.

Physical examination on admission indicated a massive head with a combination of cretinoid and adenoid characteristics. The child stood only by means of the bed railing, and at such times the posture was stooped. Mental development was definitely retarded. Psychometric examination indicated an I. Q. of 26. The head was large and rested on a short, thick neck. The abdomen was distended. The arms and legs were short and the hands and feet spade-like. The teeth were small, short, fully developed, and badly carious.

The external ocular adnexa were normal. The pupils were equal and reacted promptly to light and in accommodation. The irises appeared muddy and were of a dull-brown color. A red reflex was present, but details of the fundi could not be seen. The corneas were of normal size. The child readily followed a flashlight and apparently had no reduction in vision. With a slit lamp, the corneas presented a diffuse steamy appearance. There were scattered disc-like opacities throughout the stroma, especially centrally. The subepithelial areas were normal.

Spinal fluid examination was entirely normal. Blood cholesterol was 250 mg., serum calcium 9.9 mg., and phosphorus 3.27 mg., per 100 cc., and phosphatase was 8.6 units per 100 cc. The glucose tolerance test was normal. Roentgen studies indicated the characteristic defects of gargoylism. Hydrocephalus with diastasis of the sutures, erosion of the outer table of the skull in the occipital region, and retardation of epiphyseal development was evident. The child died at a state hospital when 7 years old.

Abnormal pathologic findings included excessive thickness of the coronary vessels and irregular plaques in the cardiac muscle. The liver was enlarged, and there were numerous sub-capsular striae present. The spleen was enlarged and its capsule focally scarred. The lepto-meninges were visibly thickened everywhere and the pia-arachnoid pronounced over the inferior surface of the cerebellar hemisphere. The pia was not adherent to the cortex. There was atrophy of the cerebral hemispheres and a compensatory hydrocephalus.

Microscopic studies showed no appreciable abnormalities with stains for fat. Characteristic changes were present in the heart. The thoracic and abdominal aorta showed intimal vacuoles with eosinophilic fibers and vacuolated areas in the media. Foamy material was present in the spleen, lungs, and liver.

Case 3.—The patient, T. C., was the younger brother of the second patient reported. He was first seen on May 14, 1946, when 20 months old, because of impaired physical and mental development, abnormal enlargement of the head, kyphosis, and inguinal and umbilical hernias. He was unable to stand. His head was long and square and was flattened anteriorly. His nose was short and stubby, and his mouth was open constantly. The abdomen was large and protruding, and umbilical and bilateral inguinal hernias were present. A funnel deformity of the chest and kyphosis were present.

On admission, 3+ acetone was present in the urine, but subsequent urinalyses were negative. Spinal fluid studies indicated no abnormality. Roentgen examination of the skull revealed diastasis of the coronal sutures and erosion of the outer tables in the occipital region. The intelligence quotient was 35.

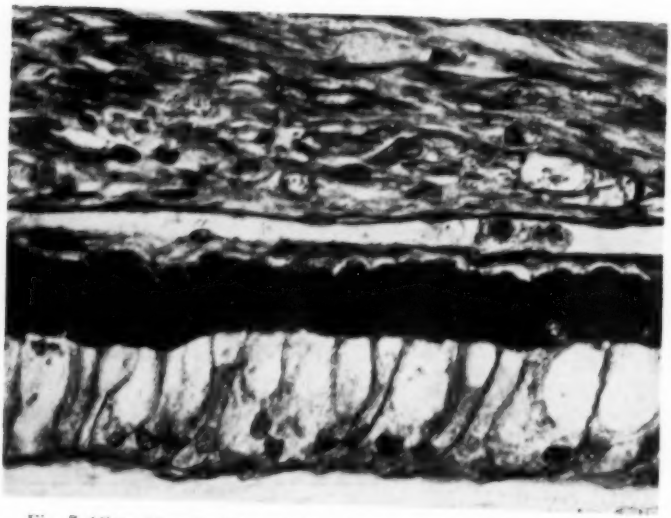

Fig. 7 (Case 1).—Swelling of the ciliary body epithelium with peripheral displacement of the nuclei. Aniline blue-orange G-fuchsin; reduced 2/5 from mag. × 540.

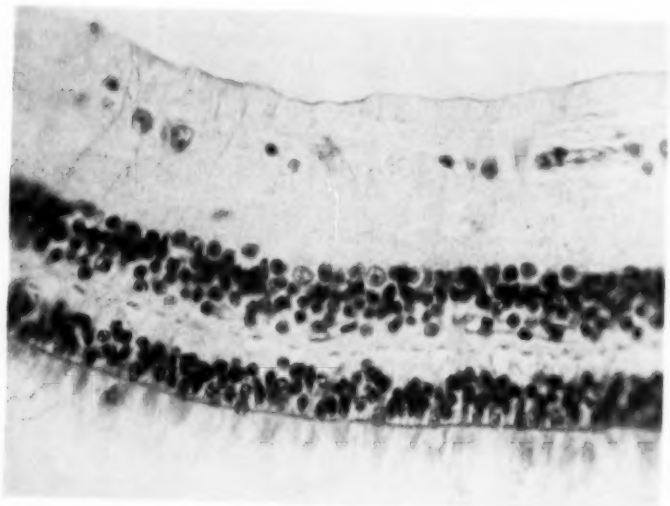

Fig. 8 (Case 1).—Swollen cells of inner nuclear layer of retina. The nucleus of many cells is displaced peripherally, and the cells are slightly larger and the cytoplasm lighter than the ganglion-like cells normally found in this layer. Nissl stain; reduced ¼ from mag. × 420.

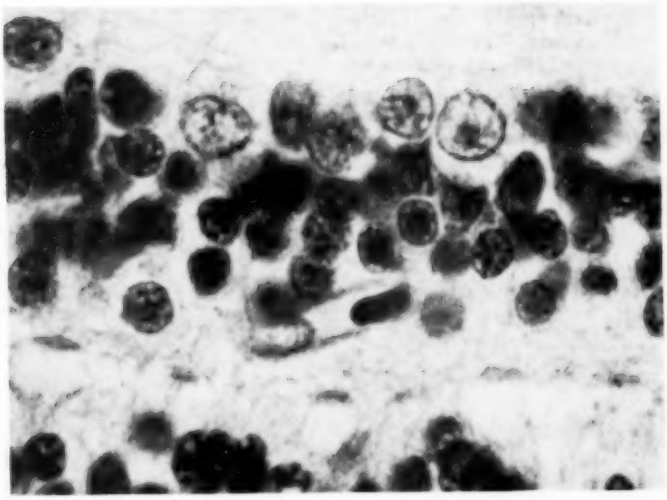

Fig. 9 (Case 1).—Higher-power view of swollen cells in inner nuclear layer. Nissl stain; reduced ¼ from mag. × 1,500.

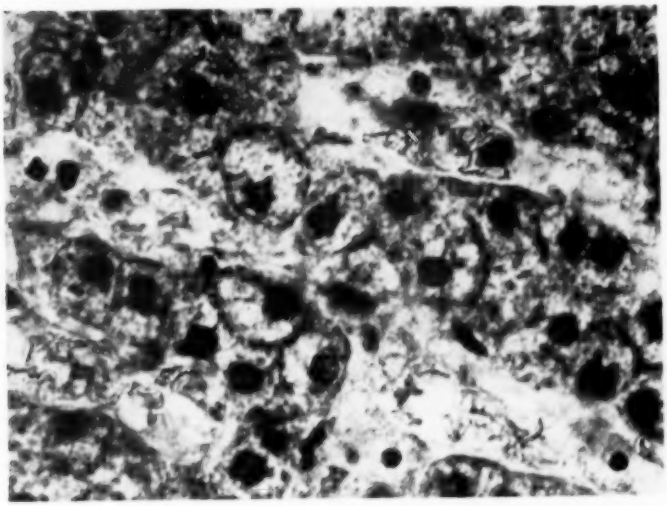

Fig. 10 (Case 1).—Swollen and vacuolated cells of the liver. Hematoxylin-eosin stain; reduced ¼ from mag. × 540.

The hemogram indicated hemoglobin 12 gm. per 100 cc.; erythrocytes 3,350,000, and leucocytes 11,500, with a differential count of 53% lymphocytes, 44% polymorphonuclear leucocytes, 3% monocytes, and 1% eosinophiles. The serum cholesterol was 272 mg., serum calcium 11.8 mg., and serum phosphorus 3.33 mg., per 100 cc. The glucose tolerance was negative. The sternal bone marrow was normal.

The ocular adnexa were normal. At the time of the initial examination the corneas appeared clear and the eyes normal. With the slit lamp, however, the characteristic disc-like opacities could be seen in the stroma. The fundi were not described.

The patient died of bronchopneumonia when 30 months old. The autopsy was performed by Dr. Eleanor Humphrey. The skull was large, with bulging frontal bossae. The teeth were few, small, and irregularly spaced. The dura was bound to deeper structures. A huge cystic tumor, formed by encapsulation of a subdural hematoma which had displaced and compressed the cerebral hemisphere, was present. The pia-arachnoid was enormously thickened and adherent in places to the cerebral hemispheres. The leptomeningeal abnormalities in this patient were reported by Magee [11] in 1950. In the frontal and temporal cortices, the most significant changes were

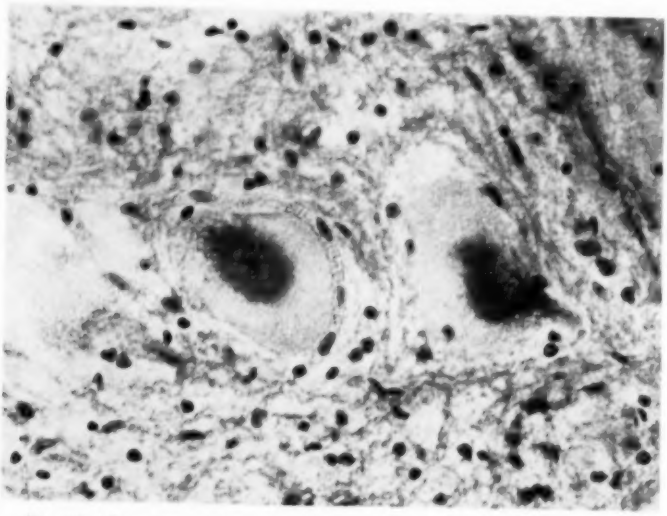

Fig. 11 (Case 3).—Swollen ganglion cells in anterior horn. Hematoxylin-eosin stain; reduced ¼ from mag. × 480.

tumefaction and ballooning of the cytoplasm of the ganglion cells, with displacement of the nuclei and the small amount of remaining mucoid substance to the periphery of the cell body. Frozen sections from the cortex stained with Sudan III, scarlet red, Nile blue, and osmic acid revealed no intercellular or extracellular staining of lipid except for a small amount of moderately thickened adventitial tissue in some of the blood vessels. Staining of frozen liver sections showed the Kupffer cells to contain some relatively insoluble carbohydrate material. Special tissue preparations by Dr. Gersh suggested the presence of some peculiar lipid. Dr. Humphreys stated that the bluish stain of many pale cells suggested a mucoid substance, but this was not stained by the Hotchkiss method except in the Kupffer cells.

OCULAR ABNORMALITIES

Clouding of the cornea is the commonest ocular abnormality in lipochondrodystrophy. This sign was first reported by Hurler [5] and is found in three of every four cases. It is sufficiently distinctive to be almost pathognomonic of the disease.

Berliner [32] reported the slit-lamp appearance of the cornea as follows:

A characteristic milky haze [is seen] with diffuse illumination.

In the youngest child . . . the earliest signs . . . were seen occupying the central areas of both corneas. The peripheral portions were only slightly infiltrated. . . . In optical section, just below the corneal epithelium, a few fine changes were observed. The infiltration began in the anterior middle layers and increased in density to the posterior corneal surface. The infiltration was seen as a collection of small punctate dots, varying in size. The deeper deposits had a yellowish hue.

Sheldon [33] described an "epithelial dystrophy" with diffuse corneal staining with fluorescein. The corneas are frequently larger than normal, and this, combined with the milky appearance, may give rise to an erroneous diagnosis of hydrophthalmos.

The eyes are widely spaced, and the orbits are shallow. Hypertelorism may be present. The eyelids are puffy and the eyelashes coarse. Vision is often reduced out of proportion to the corneal opacity, suggesting that some of the defect may be cortical or retinal.

Hatt [34] reported a case associated with congenital cataract; and Paufique, Vialtel, and Etienne [35] described retinal detachment. MacGillivray [36] reported the occurrence of strabismus, ptosis, nystagmus, and anisocoria, with a poor response to mydriatics. Monbrun and his associates [37] described a patient with buphthalmos.

Veasey [38] described in detail the ocular findings in 40 cases. In 24 patients there were abnormalities of the eyes other than infiltration of the cornea. In two cases increased intraocular pressure was found, and in these cases surgery did not affect the tension. Helmholz and Harrington [39] noted anisocoria in one case and narrowing of the palpebral fissure in another, a finding also reported by Putnam and Pelkan.[3] Engel [23] reported a Chinese boy with a hyperopia of +37.00 D. Stoeckel's [40] second case showed a coloboma of the iris. One patient of Reilly and Lindsay [20] had a pupillary membrane.

Occasional variations in the optic nerve have been recorded. Walsh [41] cites two cases, one with optic atrophy and the other with increased redness of the optic discs. In a case observed by him, both maculas were definitely edematous and the foveal reflex was absent. Hogan and Cordes' [42] first case showed papilledema, but a hydrocephalus was present. Since hydrocephalus commonly develops, it seems likely that either papilledema or optic atrophy might be a fairly constant feature of the disease.

We have found 12 pathologic descriptions of the eye in the world literature, although it is quite likely that several have been overlooked. Hogan and Cordes [42] have described two corneas and an additional entire eye; single eyes have been described by Kressler and Aegerter [43]; Berliner [32]; Rochat [44]; Zeeman [45]; Strauss [46]; Lindsay, Reilly, Gotham, and Skahen [47]; Wexler [48], and Henderson and associates.[49] Reports by François and Rabaey [50] and Wagner [51] deal with the cornea only. Unfortunately, there is no report of histopathologic study of an eye in which the cornea was not cloudy.

The corneal epithelium was described as intact by Berliner,[32] Rochat,[44] Hogan and Cordes,[42] and Wexler.[48] In the cytoplasm of the basal cells, Zeeman [45] found fine granules which stained pale violet with hematoxylin and eosin. François and Rabaey [50] noted that the basal cells of the epithelium were displaced as though they lacked support. Many of these cells were vacuolated.

In areas of cellular enlargement, Bowman's membrane was partially fragmented, but of normal appearance in those areas not adjacent to abnormal cells. The defects in the membrane were replaced by large vacuolated cells which had a granular cytoplasm. Hogan and Cordes [42] believed these granules to be partially removed in sec-

tions treated with the usual embedding techniques but retained in frozen sections. The nucleus was small, stained well (Rochat [44]), was poor in chromatin content (Strauss [46]), and somewhat eccentric.

The intracellular granules, according to Rochat,[44] were glistening and more refractile to light than the surrounding cells. Some were well outlined, and others coalesced like snowflakes.

The interlamellar spaces of the stroma were enlarged. Berliner [32] observed that the spaces were filled with a granular substance which stained pale violet with hematoxylin and eosin. Rochat [44] described fine granules in the cytoplasm of the corneal corpuscles, resembling those found in the vacuolated cells which replace Bowman's membrane. However, these granules resembled those due to postmortem changes. Zeeman,[45] Hogan and Cordes,[42] and François and Rabaey [50] considered these granules to be intracellular.

No changes have been described in Descemet's membrane. Lindsay [47] has described changes in the endothelium, with enlarged endothelial cells having a clear and vacuolated cytoplasm.

In addition to corneal changes, Lindsay and associates,[47] Wexler,[48] and Henderson and associates [49] have described scleral involvement. In Lindsay's case the sclera was thickened, and the connective tissue fibers were loosely arranged and appeared edematous and less fibrillary than normal. There were fusiform clear spaces, containing a displaced, compressed fibroplastic nucleus. A few faintly eosinophilic granules were noted in some cells. Wexler [48] described infiltration by numerous small, round, deeply staining, coarsely granular cells in the sclera. These bordered mainly in the spaces between the lamellae. The interlamellar spaces were larger than normal and contained a granular substance. Henderson and associates [49] also described the sclera as being infiltrated by small cells.

Lindsay and his colleagues [47] reported enlarged cells with a clear cytoplasm and displaced nuclei in the epithelial cells of the ciliary body, on the posterior surface of the iris, and in the inner nuclear layer of the retina. The connective tissue of the iris, ciliary body, and choroid was loosely arranged and edematous and contained numerous macrophages with granular or vesicular cytoplasm. Hogan and Cordes [42] found phagocytes in the anterior trabecular meshwork, on the anterior surface of the iris, and in the stroma of the iris in their third case.

The arachnoid surrounding the optic nerve in Wexler's [48] case showed a marked thickening and infiltration with a large number of small foam cells.

OCULAR PATHOLOGY

The right eye of the first patient and both eyes of the other two patients were removed at autopsy and fixed in Held's solution. They were mounted in celloidin and serially sectioned, and every 10th section was stained with hematoxylin and eosin. Other sections were prepared with Schiff-periodic acid stain for polysaccharides, and with aniline blue-orange G-fuchsin, Sudan IV, Best's carmine stain, cresyl violet-thionin, and toluidine blue.

As has been noted previously, the most marked changes were observed in the cornea. Bowman's membrane in many areas was split or displaced by large vacuolated cells. These cells were five or six layers thick in some areas but entirely absent in others. They were most marked near the corneoscleral limbus. Bowman's membrane did not appear destroyed by the cells, nor was it missing entirely; rather, it was divided into thin lamellae, which were so arranged that the basal layer of the epithelium never rested directly upon the vacuolated cells. These cells caused con-

siderable irregularity in height of the immediately adjacent basal cells. The total thickness of the epithelial layer was not affected. Many of the vacuolated cells appeared empty and without nuclei. When stained with aniline blue and fuchsin, others showed displaced nuclei in lightly pink-staining cytoplasm.

It should be noted that, although these vacuoles are most prominent near the limbus, the opacity seen clinically is most marked centrally. From the clinical description of these patients and from the cases in the literature, it seems probable that these vacuolated cells do not contribute materially to the corneal opacity. Additionally these cells appear to be an exception to the customary pathologic change elsewhere in the eye in not being clearly a storage phenomenon in cells normally present.

The corneal lamellae were diffusely but regularly separated, and most interlamellar spaces were optically empty. In some sections stained with aniline blue-orange G-fuchsin, a slightly pinkish material was deposited. The corneal corpuscles were diffusely swollen and filled with a reddish-staining material, which in many cases obscured the nuclei. Other cells had nuclei which were displaced peripherally by the cytoplasm.

The corneal endothelium of the first patient was vacuolated, with many cells optically empty. A few cells contained pinkish-staining cytoplasm. The changes were most marked in the central cornea, and the peripheral endothelium was normal. This change, which has been described only by Lindsay,[47] may well be a postmortem artifact. However, the vacuolation was observed in only this eye, and the changes are far more marked than usually occurs post mortem. Additionally, the patient died in the hospital, and autopsy followed death far more quickly than with the second and third patients. The corneas were of normal thickness.

The sclera was definitely less compact than usual and separated into many lamellae, some of which were filled with reddish-staining material, with the aniline blue-orange G-fuchsin stain. A few of the cells, initially described by Wexler,[45] were noted as small, compact, and deeply staining, with poorly defined nuclei.

The ciliary epithelium was hyperplastic in all eyes, especially that of the first patient. Again, however, it could not be definitely determined whether this was a postmortem change. A few of these cells were vacuolated, but most contained a homogeneous pinkish cytoplasm.

Particular attention was directed to the retina because of the regularity with which ganglion cells are involved in the brain. Retinal ganglion cells were dilated, and many appeared to have contained material which had been removed with fixation. Cells of the inner nuclear layer were abnormally enlarged, with eccentric and peripheral displacement of the nuclei. Generally these cells appeared to be larger than ganglion cells and were frequently vacuolated, with a clear space surrounding the displaced nucleus. Such cells were most frequently found in Case 1. The other layers of the retina were not abnormal.

Other portions of the eye were normal. In the right eye of the second patient a large cyst was present between the pigmented and the nonpigmented epithelium of the ciliary body.

The pia-arachnoid of the optic nerve was diffusely thickened and infiltrated with reddish-staining material, without, however, any of the minute cells present in the sclera being noted in this area. The changes in all structures were best demonstrated with aniline blue-orange fuchsin. The infiltrating substance did not stain with Best's carmine or with Hotchkiss' polysaccharide stain. The material was not lipid, at least as far as staining with Sudan IV was concerned.

THE STORAGE DEFECT

The nature of the abnormal material stored in the cell and the cellular changes in gargoylism have attracted considerable attention. Tuthill,[52] in 1934, studied the brain of one of Hurler's [5] patients and classified the defect as one of juvenile amaurotic idiocy.

Ellis, Sheldon, and Capon [7] subsequently speculated that gargoylism might belong to the group of established lipid storage diseases of cerebromacular degeneration of Niemann-Pick, Gaucher, Tay-Sachs, and Hand-Christian-Schüller.

Ashby, Stewart, and Watkin [10] analyzed the total lipids of the brain in their first case and concluded that the extracellular lipid in the perivascular region was composed largely of cerebrosides. Green [53] believed this to be the result of cerebral degenerative disease rather than related to the original substance infiltrating the neurons. Kressler and Aegerter [42] described a complete autopsy in which the generalized cellular storage was first appreciated. They suggested that the intracellular materials was a complex lipid of unknown composition.

De Lange and co-workers,[54] in 1944, suggested that the material might be a glycogen substance. In 1948, Strauss [46] found little in her material that was of lipid nature and pointed out that a nonlipid material of high molecular weight, such as glycogen, might be the stored substance.

Lindsay, Reilly, Gotham, and Skahen [47] pointed out that the lipid substance which stains could not account for the tremendous increase in volume of the cytoplasm and considered it unlikely that the substance was a lipid. Since the substance could not be stained with a variety of protein stains, it was not purely protein in nature. They found violet granules in the corneal lamellae stained with cresyl violet which suggested a mucoprotein that they also found in the liver. In specimens of liver and cartilage fixed in dioxane, trinitrophenol, formaldehyde, and acetic acid, abundant intracellular glycogen was demonstrated by the Feulgen-Bauer method. Incubation of hepatic sections with saliva, using similarly fixed hepatic tissue from a case of true glycogenosis (von Gierke's disease) resulted in the loss of the granular material, indicating that the stored material was a polysaccharide, presumably glycogen, rather than a less complex carbohydrate.

Henderson, MacGregor, Thannhauser, and Holden [49] believed that it has not been proved that the amounts of glycogen found by Lindsay and his group [47] were other than a normal quantity. In their third case, no evidence of abnormal lipid or glycogen content was demonstrated by the standard staining methods or by quantitative chemical analysis.

Brante [55] found nerve cells to be filled with gangliosides, which appeared to be the chief, if not the only, deposition. This substance contains one cerebroside part and one polysaccharide part and is the abnormal compound stored in cerebromacular degeneration. A nonlipid inclusion was present in almost all of the tissues except the nerve cells. This compound was water-soluble, formed red metachromatic precipitates with thionine, and had a composition similar to mucopolysaccharides.

In sections fixed in basic lead acetate, which preserves mucopolysaccharides, the cells were filled with metachromatic granules. In sections fixed by other substances, only the vacuoles were present, the abnormal compound having been removed in fixation.

Brante [55] suggested that the basic metabolic defect may be a congenital enzyme disturbance involving mucopolysaccharide, leading to an abnormal storage and

underdevelopment of sensitive tissues. He further suggested that the ganglioside deposition may be a consequence of the mucopolysaccharide surplus, the ganglioside being partially derived from the mucopolysaccharide.

Almost all of the tissues of the body have swelling of the cell. The cytoplasm may be clear, vacuolated, or granular. Epithelial elements, particularly of the liver, are extensively involved. The epidermis, the glands of the skin, and the anterior lobe of the pituitary gland are similarly involved. Reticuloendothelial cells, particularly in the spleen and lymph nodes, show the same clear swelling of the cytoplasm.

Mesodermal connective tissues were extensively studied by Lindsay and associates,[47] who demonstrated characteristic vacuolation and enlargement of chondrocytes, osteocytes, and fibrocytes. These authors believed that this widespread change in connective tissue was probably responsible for the malformations of the skeleton and soft tissues and the diminished growth. In the cardiac valves, the coronary arteries, and the vascular endocardium, the storage abnormality was associated with increased amounts of altered collagenous intercellular substance.

There have been few histochemical studies of the eye. Berliner [32] used formaldehyde as a fixative and stained pyroxylin sections for neutral fat. The granules of the lamellar spaces did not stain, and it was concluded that the substance was probably a lipid. No specific studies for lipids were reported, however.

Wexler [48] fixed the tissues in Bonin's solution, and sections were embedded in paraffin. These were stained with Mallory's aniline blue-orange G stain and with the Schiff-periodic acid stain but were not stained for fat. He found only a suggestion of interlamellar substance in hematoxylin-eosin-stained sections. However, in sections stained with Mallory's method, the material was abundant and appeared as red or orange-red streaks. He concluded that the deposited substance was a collagen or one of its derivatives.

François and Rabaey [50] have reported most recently on the histochemistry of the eye in gargoylism. A piece of the cornea was excised, as in keratoplasty, and one portion was fixed in 10% formalin and another in Fleming's solution. Frozen sections were made of the formalin-fixed portion, and the remainder was embedded in paraffin. In some sections the interlamellar granules showed metachromatic staining, but with toluidine blue the cytoplasm had a clear blue color without metachromasia. The osmic acid did not reveal any black or gray granules. All the reactions for lipid were negative. No staining was observed with scarlet red, Sudan III, Sudan B black, Nile blue stain, Schultze's test for cholesterol, and mucicarmine. There was no basophilic staining for granular substance with methyl blue at pH 4.7, indicating the absence of acid groups, such as the nucleic acids, which are dissociated at this pH. The corneal lamellae had a metachromatic reaction for methylene blue and toluidine blue stains. They concluded that the mucoid of the cornea does not participate in the development of the opacity.

COMMENT

A review of the literature indicates that many children with gargoylism have ocular defects other than corneal infiltration. Some of the defects arise from obvious brain disease, with optic and retinal atrophy causing decreased vision, nystagmus, strabismus, and the like. In many children, however, the decrease in vision appears to be disproportionate to the amount of corneal opacity present, and damage to the retina or to higher visual centers offers a reasonable explanation. The occasional

occurrence of buphthalmos, large corneas, and other defects suggests that these children are prone to ocular complications other than those arising purely from the storage of an abnormal substance.

Berliner, in his discussion on Wexler,[43] mentioned that he had never clinically observed the subepithelial changes which form such a dramatic histologic picture. This observation is borne out in the examination of these eyes, in which the subepithelial changes are most marked at the periphery of the cornea, with the central portion relatively clear, or at least less affected. However, clinical examination indicates that the central portion of the cornea is the more affected and that the opacities seen are much deeper in the stroma.

Henderson and his co-workers[49] pointed out that the problem concerning the identity of the abnormal substance characterizing the condition does not seem likely to be solved by the usual histologic techniques. Indeed, the results of reliable investigators using similar stains suggest that the material is not necessarily the same in all organs or in all patients. For this reason, Brante's[55] hypothesis of a deposition of a mucopolysaccharide as a primary defect with secondary infiltration of gangliosides in the central nervous system offers a particularly logical explanation. Fixation of tissues by the usual methods, particularly as is commonly done in ophthalmology, is likely to dissolve the stored substance, or at least allow most of it to escape. Thus, the fat solvents remove much of the lipids, while water-soluble materials are removed by formalin and other compounds. Gomori[56] has pointed out that even water-soluble substances are likely to be precipitated quickly to adjacent protein and be evident in the cells. This is the probable explanation of the small amount of staining material still evident.

Considerable information could be derived in future studies if the globe were first dissected rather than placed in the usual eye fixatives. Thus, the cornea could be divided into three portions, with fixation in acetone, formalin, and basic lead acetate. The remainder of the eye could be similarly dissected and fixed. While this would not yield the usual type of eye section, it would likely offer a method of learning the nature of the abnormal storage substance.

SUMMARY

A review of the literature of lipochondrodystrophy indicates an unusually large number of ocular abnormalities occurring independently of the cellular storage defect.

Three cases of lipochondrodystrophy, all familial and all with corneal infiltration, are presented. Classic subepithelial vacuolation and stromal changes were present in all. One patient presented endothelial vacuolation, not previously reported. The nature of the storage defect was not clarified by a variety of special staining methods.

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Dr. Douglas Buchanan granted us permission to report these cases; Dr. A. C. Hoops and Dr. Eleanor Humphrey removed the eyes at autopsy, and Mrs. A. E. White assisted in the preparation of the eyes.

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PREPARATION, STERILIZATION, AND PRESERVATION OF OPHTHALMIC SOLUTIONS

Experimental Studies and a Practical Method

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MEDICATIONS available to the ophthalmologist and to his patients usually are obtained from one of three sources: local pharmacies, pharmaceutical companies, and hospital pharmacies. Of these, the local pharmacies dispense by far the greatest number of preparations. On the other hand, eye medications comprise only a small part of the total volume of drugs dispensed by local and hospital pharmacists. The standards for preparing collyria in an accurate and sterile manner are generally considered to be too exacting for the average pharmacist. Unless the impetus for improved practices is provided by ophthalmologists, progress will continue to be slow. We shall demonstrate that simple, relatively inexpensive measures are sufficient to achieve accuracy of formulation and sterility of collyria, without sacrifice of drug stability or power of corneal penetration.

The irony of transmitting disease by measures intended for its prevention is abhorrent to all physicians. A growing awareness among ophthalmologists of the disease-producing role of contaminated eye medications is reflected in recent publications by Theodore,[1] King,[2] and Vaughan.[3] In view of the catastrophic results of drug-borne infections, ophthalmic medications must be prepared with aseptic precautions, sterilized after preparation, provided with an antimicrobial preservative, handled in such a way as to minimize the possibility of bacterial or viral contamination, and cultured at intervals to determine the effectiveness of these measures.

PREPARATION

The prescribing ophthalmologist has the right to expect a degree of accuracy in keeping with U. S. P. standards, namely, within ±5%.[4] This demand is reasonable in view of the potency of the drugs involved, whereby systemic absorption can have serious consequences. Balances and weights should be accurate within these limits to weigh the small quantities involved. Measuring devices should be appro-

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priate in size for the volumes to be measured. Disregard of these considerations, we think, is part of the answer to the ophthalmologist's query why all too often simple collyria, such as zinc sulfate with boric acid, are too irritating for the patient to use.

Only those ingredients in a proper state of preservation should be used. Particular attention should be paid to salts which carry several moles of water of hydration. Zinc sulfate U. S. P. is almost one-half water by weight. The use of this salt in the fully effloresced state practically doubles the intended concentration of active ingredient. This could mean the difference between an acceptable eye solution and a distinctly irritating one. Scopolamine hydrobromide is about one-eighth water by weight. Use of an effloresced salt of this powerful alkaloid would increase the actual concentration of scopolamine by about 12%. Under certain circumstances such an increase might have harmful results.

The principles governing penetration of drugs through the cornea into the aqueous humor have been elucidated by Cogan and his co-workers * and by Swan and White.[7] Passage of dissolved substances is presumed to be a function of phase solubility. The epithelium and endothelium are permeable to lipid-soluble and nonpolar compounds, but not to electrolyes or substances that are exclusively soluble in water. The reverse is true of the corneal stroma. For a substance to pass completely through the intact cornea, it must possess both water and lipid solubility or exist in phases meeting these requirements.

Some of the more important agents used in ophthalmology, including certain alkaloids, are weak electrolytes. Salts of these bases, rather than the bases themselves, are used because of their greater solubility in water, as well as their greater stability. Within a range peculiar to each base, these salts progressively dissociate, with decrease in hydrogen ion concentration. Eventually a point is reached at which the free base is precipitated. In the form of free base most alkaloids are fat-soluble and variously water-soluble. On the other hand, these and other organic electrolytes as salts are all water-soluble, and most are lipid-insoluble. Only those substances which possess both water and lipid solubility will penetrate the cornea.

The interrelationship of hydrogen ion concentration, equilibrium concentration of free base, and chemical stability has been well brought out by Hind and Goyan.[8] At the slightly alkaline pH of the tears, increased availability of free base is more than offset by lack of chemical stability and by irritating properties of the free base. A shift of the reaction toward the acid side, while reducing the concentration of free base, increases stability and reduces irritation. These authors use a series of buffer systems to regulate the pH of various groups of collyria.

The passage of alkaloids across the corneal barrier was quantitatively studied by Cogan and Hirsch.[5] They found increased transfer of atropine, pilocarpine, and ephedrine with increase in pH. When a given electrolyte is dissolved in distilled water, the pH of the resulting solution is determined by the properties and concentration of that electrolyte. The pH of simple solutions of most alkaloidal salts lies between 4.0 and 5.0, that is, in a range where the compounds are stable. For reasons of increasing stability, therefore, it is seldom necessary to adjust the pH by added buffer. When a drop of an unbuffered solution is instilled into the conjunctival sac, the buffering action of the tears almost instantly adjusts the pH to neutrality or slight alkalinity, thereby making available an increased concentration of free base

* References 5 and 6.

for penetration into the corneal epithelium. Any buffer system used to alter the pH of the alkaloidal solution will inevitably interfere with the buffering action of the tears, and thus reduce the amount of free base available for absorption. For this reason, as well as for reasons of simplicity and economy, we recommend that the use of buffers be avoided whenever possible and that only substances of low buffering capacity be used when it is necessary to use a buffer at all. It is assumed that only chemically clean glass containers, free of residual detergent substances, will be used.

Although we have not studied experimentally the effects of osmotic properties of collyria, the empirical use of solutions adjusted approximately to the tonicity of 1.3% sodium chloride has proved to be entirely satisfactory in our experience.

STERILIZATION

Sterilization of collyria has been a problem hitherto unsolved by most local pharmacies. Morrison and Truhlsen [9] reviewed various methods, including autoclaving, and found experimentally a variable loss of physiologic activity after one or more exposures of collyria for 15 minutes to steam under pressure at 121 C. It is to be noted that their experiments were done with solutions buffered on the alkaline side of neutrality. On the other hand, Murphy and Stoklosa,[10] using unbuffered alkaloidal salts at an acid pH, found negligible chemical degradation after autoclaving at 121 C. for time intervals appropriate to the size of the containers used. Theodore and Feinstein [11] advocate the use of filtration under pressure for commercially manufactured preparations. This method, although effective, is not adaptable for use by smaller pharmacies. We shall show that autoclaving under the proper conditions of time and pH does not result in significant degradation of the principal drugs used in ophthalmology.

PRESERVATION

Since no known preservative harmless to ocular tissues and compatible with ophthalmic drugs has virucidal or rapidly bactericidal properties, the importance of careful technique in the use of medications cannot be overemphasized. In addition, an antimicrobial substance must be incorporated in ophthalmic formulas. The ideal preservative agent for this purpose would be one possessing to the highest degree the following properties:

1. Bacteriostatic and fungistatic power. This must be demonstrated specifically against Pseudomonas aeruginosa (Bacillus pyocyaneus), must be maintained in the presence of other active ingredients, and must not be inactivated by autoclaving.

2. Tissue tolerance. The preservative must not be irritating to the cornea or conjunctiva on repeated application. No epithelial damage should be demonstrable in the concentration used. Moreover, if there is any likelihood that the preparation may be used in the operating room, the preservative must be harmless to the intraocular tissues as well.

3. Low sensitizing power. Since patients may use certain medications over a period of months or years, the preservative used must have a low incidence of sensitization. This can only be determined by long clinical experience.

4. Compatibility with active ingredients.

5. Chemical stability.

All the above properties should be maintained under the conditions of use in actual practice. The most important of these is hydrogen ion concentration.

Although various compounds have been strongly advocated for use as preservatives, we know of no previous comparative study of the chemical and antibacterial behavior of these compounds with respect to numerous species and strains of organisms under various physical and chemical conditions. The selection of preservatives to be tested was based on a consideration of the properties listed above. Chlorobutanol and phenylmercuric nitrate are widely used and fulfill many of the requirements for the ideal preservative. Phenylethyl alcohol has recently been suggested as a possible preservative by Brewer, Goldstein, and McLaughlin [12] on the basis of its activity against Gram-negative bacteria.[13] Benzalkonium (Zephiran) chloride, because it has been widely used and is still recommended by some, was included in this study, notwithstanding its tendency to be inactivated by other compounds present,[14] irritation of ocular tissues in bactericidal concentrations,[15] diminished effectiveness at an acid pH range,[16] and incompatibility with certain anions, notably nitrate, salicylate, and fluorescein ions. The concentrations tested were those generally used for preservative effect in collyria. Chlorobutanol and phenylethyl alcohol, each in 0.5% concentration, were compared with phenylmercuric nitrate 1:25,000.

EXPERIMENTAL STUDY

The purpose of the laboratory studies reported here was threefold. First, it seemed desirable to determine whether and under what conditions solutions of the principal ophthalmic drugs would withstand autoclaving. Second, it was desired to assess and compare the antibacterial properties of the substances commonly recommended as preservatives for collyria. Third, a comprehensive survey was undertaken to determine the effectiveness of the system in use at our hospital.

Materials

All drugs used in these experiments conformed to U. S. P. or N. F. standards. The boiling point of phenylethyl alcohol was 219 C.

Soft-glass collyrium bottles,† capacity 7.5 cc., were used as containers for the solutions during the tests.

The bottles were sealed with phenolic resin screw caps containing natural rubber liners.‡

Freshly distilled water, pH approximately 6.0, was used for all solutions.

Strains of the various organisms were obtained by isolation in our laboratory from clinic and private patients. One of the Pseudomonas strains was recovered from a corneal ulcer; several others were isolated from conjunctival exudates. Most of the strains, however, were obtained from ear, nose, or throat sources. The behavior of the eye strains with respect to the compounds studied did not differ from that of the others.

The stock culture medium was meat infusion broth, freshly prepared in our laboratory. Plates were poured from this with the addition of 2% agar and 5% horse blood. Sugars were added by weight to make the appropriate concentrations. Mannitol was used in the concentration usually added to scopolamine solutions. Other media were Brewer's liquid thioglycollate medium, Sabouraud's broth, and Mueller's starch agar.

Methods

All experiments in this study were repeated several times, and the results are considered to be reproducible.

All pH determinations were done with a Beckman Model G pH meter.

† Pennsylvania Glass Company, Pittsburgh.

‡ Armstrong Cork Company, Lancaster, Pa.

Spectrophotometric determinations were done in the ultraviolet range with a Beckman D U quartz spectrophotometer in 1 cm. cells.

Proximate assays were performed according to U. S. P. methods, using a Watkins continuous alkaloidal extractor.[17] All assays were run in duplicate, so that each Table represents the average of two or more determinations for each lot tested. More than one lot of each type of collyrium was tested.

Collyria were sterilized by autoclaving in their own sealed glass bottles at 121 C. for five minutes. This temperature was recorded by a thermometer placed in the autoclave with the bottles of collyria.

Cultures were incubated aerobically at 37 C. They were read at 48 hours or longer. Delayed growth appearing after 48 hours was not observed when cultures were incubated for longer periods. The identity of cultures in broth was checked by observation of characteristic growth and by periodic plating on blood agar and starch agar.

Two methods of contaminating collyria were employed. In the earlier experiments, surface colonies from agar plates were suspended in a small amount of sterile saline. The crude suspension was then homogenized by mechanical grinding in a Pyrex tube with a rotating glass pestle. One drop of the homogenized suspension was instilled from a Pasteur pipette into each bottle of test solution. The second, and simpler, method consisted of using one drop of undiluted broth culture to contaminate the solution bottles. No attempt was made to standardize the size of the drops or the density of the inocula. Neither these factors nor the age of the cultures appeared to influence the results.

In testing for residual contamination of collyria, parallel cultures on blood agar and in broth were done in the earlier experiments. These revealed that inoculation of 0.1 cc. of solution into 5 cc. of broth was a more sensitive test for surviving bacteria than inoculation of a similar quantity onto the surface of an agar plate. For this reason, only broth tubes were used in subsequent tests. Transfers from solutions containing phenylmercuric nitrate were made into liquid thioglycollate medium in order to neutralize adsorbed traces of the mercurial compound. All strains grew well on the media used. All strains of Ps. aeruginosa, also, grew well in a 10% enzymatic hydrolysate of casein at pH 5.5.

Tests for bacteriostatic effect were performed by inoculation of one loopful of broth culture into tubes of nutrient broth containing the preservative in the concentration to be tested. Presence or absence of growth was noted at 48 hours. Subcultures of negative tubes were done by transferring 0.5 cc. into 5.0 cc. of liquid medium containing no preservative. However, subcultures were not done routinely when a bacteriostatic effect was observed in the primary series of tubes.

All comparative experiments were run simultaneously, with parallel controls of each strain and each solution. Controls of collyria without preservatives were not included after it had been shown that organisms survived in these indefinitely. However, a saline control of the inoculum was always included as a check on viability.

A survey was undertaken of all open bottles of collyria in use wherever they could be found in our hospital. A total of 576 individual bottles, representing more than 30 different drugs and including 27 bottles of fluorescein, were cultured in thioglycollate broth by the method already outlined.

Results

When distilled water with an initial pH of 6.0 was autoclaved at 121 C. for five minutes in soft-glass bottles, the pH after autoclaving was found to have risen to 9.10. Titration of a 50-cc. pooled sample of this water with 0.02 N sulfuric acid in the presence of methyl orange required 0.63 cc. of acid to reach an end-point. This amount of acid corresponds to 0.013 mEq. of sodium carbonate in 50 cc., or 0.0019 mEq. in 7.5 cc. of water.

The same containers were again filled with freshly distilled water at a pH of approximately 6.0, sealed as before, and reautoclaved at 121 C. for five minutes. The pH of the water after sterilization was found to be 8.4. A pooled sample of 50 cc. was titrated as before and found to contain 0.003 mEq. of sodium carbonate, or 0.00045 mEq. per 7.5 cc.

To determine whether the relatively small amount of alkali transferred from the glass to the water would have a significant degrading effect on the alkaloidal solutions to be sterilized in these containers, various collyria were prepared according to the formulae in Table 1. These collyria were checked for pH and assayed before autoclaving, immediately after autoclaving, and after 1, 3, 6, and 16 months of storage at an average temperature of about 25 C. The results recorded in Tables 2 and 3 indicate that when solutions of atropine, eucatropine, homatropine, pilocarpine, and scopolamine were subjected to this treatment, no significant change

TABLE 1.—*Formulas of Collyria Tested in Experiments*

Tetracaine hydrochloride	0.5 gm.	Physostigmine salicylate	0.5 gm.
Chlorobutanol	0.5 gm.	Chlorobutanol	0.5 gm.
Sodium chloride	1.2 gm.	Sodium bisulfite	0.1 gm.
Dist. water q. s. ad	100.0 cc.	Boric acid	2.2 gm.
		Dist. water q. s. ad	100.0 cc.
Atropine sulfate	1.0 gm.	Atropine sulfate	4.0 gm.
Chlorobutanol	0.5 gm.	Chlorobutanol	0.5 gm.
Sodium chloride	1.1 gm.	Sodium chloride	0.7 gm.
Dist. water q. s. ad	100.0 cc.	Dist. water q. s. ad	100.0 cc.
Homatropine hydrobromide	2.0 gm.	Scopolamine hydrobromide	0.2 gm.
Chlorobutanol	0.5 gm.	Chlorobutanol	0.5 gm.
Sodium chloride	0.9 gm.	Mannitol	3.0 gm.
Dist. water q. s. ad	100.0 cc.	Dist. water q. s. ad	100.0 cc.
Eucatropine hydrochloride	4.0 gm.	Phenylephrine hydrochloride	10.0 gm.
Chlorobutanol	0.5 gm.	Chlorobutanol	0.5 gm.
Sodium chloride	0.6 gm.	Sodium bisulfite	0.3 gm.
Dist. water q. s. ad	100.0 cc.	Dist. water q. s. ad	100.0 cc.

TABLE 2.—*Determinations by Method of Alkaloidal Extraction**

Solution		Atropine Sulfate		Atropine Sulfate		Eucatropine Hydrochloride		Homatropine Hydrobromide	
		pH	Assay	pH	Assay	pH	Assay	pH	Assay
Before autoclaving		4.3	1.010	4.9	3.969	4.4	4.058	4.7	2.008
Months after autoclaving	0	2.9	0.999	2.7	3.953	2.9	3.998	2.6	1.999
	1	3.6	0.986	3.5	3.930	4.3	4.079	3.9	1.948
	3	4.3	1.010	4.3	3.988	4.2	3.957	4.1	2.023
	6	5.7	0.997	...	.....	4.4	4.088	...	.....
	11	...	.....	5.2	3.889	...	.....	...	.....
	12	5.2	1.020	...	.....	...	.....	...	.....
	13	...	.....	...	.....	4.3	3.904	4.0	2.107

* Assays in grams per 100 cc.

in potency occurred. Stability was maintained during periods of storage of at least 14 months.

Table 3 indicates that solutions of phenylephrine were stable for a period of at least three months after heat sterilization. The only evidence of degradation at the end of this time was a slight change to a pink color. Tests for the presence of sulfite ion in the formula after three months were negative, showing complete oxidation of sulfite to sulfate. The possibility of prolonging the stability of these solutions by increasing the sulfite content of the formula is being explored.

Table 4 indicates that 0.5% solutions of physostigmine salicylate are stable for at least several months; the only change at the end of seven months was a very slight discoloration. Analysis of this solution also revealed absence of sulfite ion. Here, again, studies are under way to determine whether increasing the sulfite content will prolong stability.

Solutions of tetracaine showed no significant degradation at the end of six months. No further assay was done until the end of 14 months, at which time significant degradation was found. Studies are in progress to ascertain at about what time interval degradation becomes significant. The results are recorded in Table 4.

Since the pH of chlorobutanol solution falls after autoclaving, and because an autoclaved solution gives a positive test for chloride ion, it is concluded that hydrolysis of chlorobutanol occurs during sterilization. To determine the degree of hydrolysis occurring at various hydrogen ion concentrations, 0.5% solutions of chlorobutanol were prepared in citric acid-sodium phosphate buffers in 100 cc.

TABLE 3.—*Determinations by Method of Alkaloidal Extraction**

Solution		Pilocarpine Hydrochloride		Scopolamine Hydrobromide		Phenylephrine Hydrochloride		
		pH	Assay	pH	Assay	pH	Assay	
Before autoclaving		4.0	3.886	4.5	0.301	4.7	9.717	
Months after autoclaving	0	3.0	3.795	2.8	0.301	2.7	9.717	
	1	2.9	3.790	4.6	0.310	3.6	9.717	
	3	3.9	3.767	5.0	0.304	4.4	9.757	(slight change in color)
	11	4.3	3.679	...	.....	...	.....	
	14	...	.....	5.2	0.296	...	.....	

* Assays in grams per 100 cc.

TABLE 4.—*Determinations by Spectrophotometric Method**

Solution		Physostigmine Salicylate		Tetracaine Hydrochloride		Scopolamine Hydrobromide		Homatropine Hydrobromide	
		pH	Assay	pH	Assay	pH	Assay	pH	Assay
Before autoclaving		4.0	0.497	5.0	0.479	5.3	0.294	4.7	2.003
Months after autoclaving	0	3.2	0.497	3.4	0.477	5.3	0.294	3.8	2.003
	1	...	.....	5.7	0.481	...	.....	3.8	2.000
	2	3.0	0.497	...	.....	...	.....	...	.....
	3	...	.....	5.6	0.484	...	.....	...	.....
	6	...	.....	5.8	0.474	...	.....	...	.....
	7	5.2	0.480†	...	.....	...	.....	...	.....
	9	...	.....	...	.....	5.4	0.311	4.5	2.000
	14	...	.....	5.6	0.466‡	...	.....	...	.....

* Assays in grams per 100 cc.
† Solution slightly pink.
‡ Significant degradation.

tightly stoppered glass bottles. The chlorobutanol was dissolved with the aid of magnetic stirrers, using Teflon-coated magnets. The solutions were autoclaved in the same bottles at 121 C. for different periods of time. Titration for chloride ion with standard silver nitrate solution was carried out according to the U. S. P. modification of Volhard's method. Table 5 shows that hydrolysis of chlorobutanol is slight at pH values below 5.0 but increases sharply in less acid solutions. Since liberation of chloride ion reduces the pH of unbuffered solutions, hydrolysis of chlorobutanol tends to be self-limited. The autoclaved solutions were not irritating to the eyes of human volunteers. The results are recorded in Table 5.

It is apparent from the Tables accompanying the text that all compounds studied exerted an antibacterial effect against the Pseudomonas strains used in these experiments. Table 6 represents the protocol of a single experiment. It suggests that the

effect of these compounds is not only bacteriostatic, but even bactericidal over a 24-hour period of exposure. Actually, out of a large number of trials, rare instances occurred of growth in tubes containing chlorobutanol, phenylmercuric nitrate, and phenylethyl alcohol in the concentrations listed. In the case of chlorobutanol, these failures were rare and sporadic. No instance was observed in which a single strain was able to grow consistently on serial transfer in chlorobutanol broth, the first subculture being invariably negative. The incidence of growth in the presence of phenylethyl alcohol 0.5% was less fortuitous, in that strains 4K and 32S were able to grow consistently on serial transfer in phenylethyl alcohol broth. Successful

TABLE 5.—*Percentage Hydrolysis of Buffered 0.5% Chlorobutanol Solutions Before and After Sterilization at 121 C.*

Before Sterilization		After Sterilization								
0 Min.		5 Min.		10 Min.		15 Min.		20 Min.		
pH	%	pH	%	pH	%	pH	%	pH	%	Buffer
Time at 121 C.										
2.6	0	2.5	0.6	2.5	2.4	2.4	3.3	2.3	3.3	0.02 M citric acid 0.04 M sodium phosphate
3.0	0	3.0	1.8	3.0	2.4	2.9	2.4	2.8	4.1	Same as above
4.0	0	3.9	1.8	3.9	2.4	3.7	2.4	3.6	4.1	Same as above
5.0	0	4.8	2.4	4.7	4.7	4.4	5.3	4.3	7.7	Same as above
6.0	0	5.7	13.0	5.7	16.3	5.4	26.7	5.4	30.2	0.1 M citric acid 0.2 M sodium phosphate
7.0	0.6	6.4	52.2	6.4	61.7	6.1	74.0	6.1	78.8	Same as above
8.0	1.8	6.3	61.7	6.3	69.0	6.1	76.0	6.0	79.4	0.05 M citric acid 0.1 M sodium phosphate
8.0	2.4	6.8	62.7	6.6	88.9	6.6	92.4	6.6	94.4	0.1 M citric acid 0.2 M sodium phosphate

TABLE 6.—*Growth of Pseudomonas in Nutrient Broth, ph 7.4 to 7.6*

	(35 Strains)	
	Primary	Subculture into Thioglycollate
Control	35/35	....
Chlorobutanol 0.5%	0/35	0/35
Phenylmercuric nitrate 1:25,000	0/35	0/35
Phenylethyl alcohol 0.5%	2/35	2/35

passage was not obtained in phenylmercuric nitrate broth, nor were static organisms recovered from it in thioglycollate broth.

When broth containing chlorobutanol 0.5% was autoclaved in sealed containers at 15 lb. pressure for 10 minutes, the hydrogen ion concentration increased, presumably because of hydrolysis of chlorobutanol. Although the broth became slightly turbid, no growth was obtained in the autoclaved broth, as shown by negative subcultures in plain broth. The results are shown in Table 7. Strain 4K again demonstrated its ability to grow in phenylethyl alcohol broth.

As seen in Table 8, addition of fluorescein sodium to chlorobutanol broth interfered with the bacteriostatic effect of the latter upon Pseudomonas strains. This effect is considered to be due to degradation of chlorobutanol at higher pH values.

That phenylethyl alcohol is not an effective bacteriostatic agent against Gram-positive species has already been mentioned and is confirmed by the data presented in Table 9.

Eight strains of Candida were completely inhibited by chlorobutanol 0.5% in Sabouraud's broth. Controls of each strain grew readily in plain Sabouraud's broth. Two strains of Aspergillus niger were likewise inhibited.

Four strains of Proteus vulgaris which grew readily in ordinary media were inhibited in the presence of chlorobutanol 0.5% and phenylethyl alcohol 0.5%.

TABLE 7.—*Growth of Pseudomonas in Broth*

(10 Strains)	Unautoclaved		Autoclaved		
	pH	Growth/Strains	pH	Growth/Strains	Subculture
Broth control	7.0	10/10	...	.....	.....
pH control	...	.....	5.5	10/10	.....
Chlorobutanol 0.5%	6.2	0/10	5.5	0/10	0/10
Phenylethyl alcohol 0.5%	6.5	1/10	6.7	1/10	.....

TABLE 8.—*Growth of Pseudomonas in Broth*

(10 Strains)	pH	Growth/Strains
Broth control	7.4	10/10
Chlorobutanol 0.5%	6.9	0/10
Chlorobutanol 0.5% and fluorescein 2.2%	7.4	3/10

TABLE 9.—*Growth of Staphylococcus Aureus in Broth*

(10 Strains)	Growth/Strains
Control	10/10
Cholorobutanol 0.5%	0/10
Phenylethyl alcohol 0.6%	4/10

TABLE 10.—*Growth of Pseudomonas in Different Media*

(22 Strains)	Control		With Chlorobutanol 0.5%	
	pH	Growth	pH	Growth
Infusion broth	7.4	22/22	7.5	0/22
1% dextrose broth	7.0	22/22	7.1	0/22
	7.0	5/5	7.1	1/5*
Thioglycollate broth	7.3	22/22	7.2	1/22*
1% mannitol broth	7.7	5/5	7.6	0/5
8% mannitol broth	6.9	10/10	6.9	0/10

* Not repeatable.

As shown in Table 10, the bacteriostatic effect of chlorobutanol was demonstrated in the presence of various sugars and reducing substances. Two isolated instances of growth could not be repeated in the same media.

Phosphate-citrate and phosphate buffer systems containing chlorobutanol 0.5%, when heavily contaminated with Pseudomonas organisms, tended to become sterile within a 24-hour period. This tendency was apparent over a pH range from 3.0 to 8.0. At the lowest pH values, death of some controls was presumed to be due to acidity alone. When neutral or alkaline solutions of sufficiently high buffering capacity were autoclaved in the presence of chlorobutanol, the antibacterial effect

of the latter was definitely impaired. It was presumed that chlorobutanol had been hydrolyzed by heat at these higher pH values. In the more acid pH range, up to pH 6.0, autoclaving did not inactivate the antibacterial effect of chlorobutanol. The results of these experiments are summarized in Table 11.

As shown in Table 12, comparative tests of the antibacterial effect against 15 strains of Pseudomonas of the three test substances after autoclaving in phosphate buffer pH 5.0 demonstrated an apparent superiority of chlorobutanol.

Tetracaine 0.5% proved rapidly toxic to Pseudomonas organisms, as evidenced by the appearance of negative cultures in most instances within 20 minutes after the introduction of a contaminating drop of broth culture or saline suspension of

TABLE 11.—*Survival of Pseudomonas in Buffer Solutions*

(9 Strains)						
pH	3	4	5	6	7	8
Buffer controls	2/5	5/5	9/9	9/9	9/9	8/9
Chlorobutanol 0.5%, autoclaved	0/5	0/5	0/9	0/9	9/9	9/9
Chlorobutanol 0.5%, unautoclaved	...	...	0/4	0/4	0/4	0/4

TABLE 12.—*Twenty-Four Hour Survival of Pseudomonas in Autoclaved Phosphate Buffer ph 5.0*

(15 Strains)	
	Survival/Strains
Control (no preservative)	15/15
Chlorobutanol 0.5%	0/15
Phenylmercuric nitrate 1:25,000	2/15
Phenylethyl alcohol 0.5%	3/15

TABLE 13.—*Twenty-Four Hour Survival of Pseudomonas in Sodium Fluorescein 2.2%, Unautoclaved*

	pH	Survival/Strains
Control	7.2	6/6
Chlorobutanol 0.5%	7.3	1/6
Phenylmercuric nitrate 1:25,000	7.4	2/6
Phenylethyl alcohol 0.5%	7.3	1/6

bacteria. Addition of benzalkonium chloride did not enhance the bactericidal effect of tetracaine.

As has been mentioned, the antibacterial effect of chlorobutanol is destroyed by autoclaving in the presence of sodium fluorescein. Table 13 shows that when unautoclaved aqueous solutions of fluorescein were contaminated with Pseudomonas, none of the test preservatives was able consistently to sterilize the drug solution within 24 hours. Instances of 72-hour survival in 2.2% sodium fluorescein were recorded for each of the preservatives studied. As has been mentioned, benzalkonium chloride is incompatible with fluorescein.

When collyria other than fluorescein, unbuffered and containing chlorobutanol 0.5%, were autoclaved in sealed soft-glass bottles, a fall in pH was noted, but the antibacterial effect of chlorobutanol was not inactivated. The theoretical basis for this observation has been presented. The results are recorded in Table 14.

The bactericidal effect of benzalkonium chloride was decidedly variable, in that survival often occurred in lower dilutions when higher dilutions were sterile. Even

in the region of neutrality or slight alkalinity, benzalkonium did not appear to be a uniformly effective bactericide, as seen from Table 15. We are currently exploring its anti-Pseudomonas effect at lower pH values.

Comment

The technique employed in the experimental studies constituted a severe challenge to the antibacterial properties of the test substances. Plate counts showed that the inocula contained several million organisms. It is inconceivable that in actual practice any such degree of contamination would occur. Obviously, no pharmaceutical preparation offers any more favorable opportunity for bacterial growth than the culture media used in our tests.

It is not our intention to claim bactericidal powers for any of the compounds tested, even though subcultures showed that solutions and media containing these

Table 14.—*Twenty-Four Hour Survival of Pseudomonas in Autoclaved Collyria*

	pH After Autoclaving	Per Cent Chlorobutanol	Survival/Strains
Saline control	5.8	0.0	4/4
Distilled water	4.8	0.5	1/4*
Atropine sulfate 1%	3.4	0.5	0/4
Pilocarpine HCl 1%	5.5	0.5	0/4
Scopolamine HBr 0.3%	3.4	0.5	0/4
Zinc sulfate 0.1%	4.1	0.5	0/4
Physostigmine salicylate 1%	3.9	0.5	0/4
Fluorescein sodium 2%	7.2	0.5	4/4†
Homatropine HBr 1%	4.4	0.5	1/9‡
Phenylephrine HCl 10%	3.8	0.5	0/9

* Negative at 48 hours.
† Positive at 48 hours.
‡ Negative at 72 hours.

Table 15.—*Twenty-Four Hour Survival of Pseudomonas in Benzalkonium (Zephiran)*

Dilution	pH	Survival/Strains	Per Cent
1:50,000	7.65	6/10	60
1:25,000	7.5	3/13	23
1:10,000	7.4	5/30	16
1:5,000	6.9	3/33	9

preservatives usually became sterile over a period of 24 hours. For practical purposes, any substance which is consistently bacteriostatic and fungistatic should be sufficient to maintain sterility of ophthalmic collyria when these are properly handled.

On the basis of antibacterial properties alone, phenylethyl alcohol 0.5% was shown to be inferior to the other two substances, in that two strains of Pseudomonas could be serially transferred in its presence. Its ineffectiveness against Gram-positive organisms was confirmed by us in a limited trial. Unless phenylethyl alcohol were shown to have superior bacteriostatic qualities, there would hardly exist an incentive for proceeding with investigation of such properties as its tolerance by ocular tissues.

Because of adsorption phenomena, bactericidal properties cannot be attributed to mercurials unless subcultures are inoculated into thioglycollate broth or some other medium capable of neutralizing traces of the compound adhering to transferred bacteria and exerting a continued bacteriostatic effect upon them. Evaluated

in this manner, phenylmercuric nitrate was a good bacteriostatic substance but was not rapidly bactericidal in a dilution of 1:25,000. As in the case of chlorobutanol, rare failures of bacteriostasis were noted. On the basis of comparative experiments, phenylmercuric nitrate appeared sometimes equal, sometimes inferior, to chlorobutanol in the respective concentrations used.

The broad spectrum of chlorobutanol is reflected in its effectiveness on repeated testing against both Gram-positive and Gram-negative bacteria, as well as two species of fungi, or molds. While sporadic unexplained failures occurred with this, as with phenylmercuric nitrate, it was never possible by the method of survivor selection to obtain serial subcultures in chlorobutanol broth. In comparative tests, the performance of chlorobutanol 0.5% was never inferior, usually equal, and occasionally superior to that of phenylmercuric nitrate 1:25,000.

The present study indicates that none of the compounds tested can be implicitly depended upon to guarantee the sterility of alkaline solutions, such as fluorescein.

Practical Method for Smaller Pharmacies

In the light of the evidence presented, simple methods will provide satisfactory collyria. The equipment needed can be utilized for other pharmaceutical procedures as well. The following items are considered essential:

Autoclave, cabinet, electrically heated, 22 in. wide, 16 in. deep, 37 in. high. Cost, about $250.

Water still, electrically heated, 1 gal. per hour capacity. Cost, about $100. Gas-heated stills are available in the same price range.

Balance, student's analytical, sensitive to 0.1 mg. Cost, about $100.

Weights, fractional, student's, for the balance. Cost, about $5.

Glassware: 3 fritted funnels, 150 cc., Buchner type, Corning #36060, coarse frit; 2 aspirator bottles, 250 cc., Corning #1220; 3 sealing tubes with fritted discs, Corning #39580, coarse frit. Total cost, under $40.

Filter pump, water, with antisplash attachment. Total cost, $5.

Magnetic stirrer with coated magnets. Cost, $35.

Procedure.—Chlorobutanol 0.5% solution is made in distilled water taken directly from the still. To expedite dissolving, obviate loss of chlorobutanol, and prevent absorption of contaminated air, the solution is stirred magnetically in a stoppered bottle or flask. Other ingredients are weighed and added to the chlorobutanol solution in a glass-stoppered mixing cylinder. The solution is then filtered through the fritted glass-funnel assembly equipped with air filters in the suction line. Three seperate funnel assemblies should be available. One is to be used exclusively for the filtration of mydriatics and should be plainly marked for easy identification. This is necessary because of the possibility that a small amount of drug might be trapped in the funnel after cleaning. Sollmann [18] states that atropine in 1:100,000 solution produces a definite mydriatic effect; atropine contamination of other solutions must therefore be avoided. A second funnel assembly should be reserved for filtering miotics only, and so marked. The third funnel assembly should be used for all other solutions. Figure 1 shows a completely assembled unit.

After filtration is complete, the solution is allowed to flow by gravity through the plastic tubing attached to the tubulure of the aspirating bottle into the glass containers. The containers are tightly closed with their rubber-lined screw caps, and autoclaved at 121 C. for five minutes. The pressure must be reduced slowly to prevent bursting of bottles. When cool, the bottles should be labeled for positive identification of their contents.

In the interests of greater accuracy and economy of time, it is desirable to prepare several bottles of a collyrium at one time. The number will be governed, of course, by the frequency of demand. In this connection, it should be pointed out that these solutions can be preserved for a greater period of time by storage in the frozen state. Sufficient air space in the bottle should be provided for expansion of the frozen solution.

In the event that a prescription is intended for one particular patient, which would require a dropper-bottle unit, the accompanying dropper top can be stapled into a stiff paper envelope and autoclaved separately.

A retail pharmacist in a community, by adopting these techniques, may attract prescriptions from several ophthalmologists and develop a reputation of specializing in eye medications. The cost of the equipment necessary to prepare reliable medications is hardly to be compared with that of the apparatus used for dispensing refreshments in most drugstores.

CLINICAL EXPERIENCE

Regardless of experimental evidence, no method can be considered proved unless it has been tested in actual practice. In an effort to determine whether the use of chlorobutanol 0.5% in combination with careful technique is really effective in preventing bacterial contamination, all bottles of collyria in use in our hospital

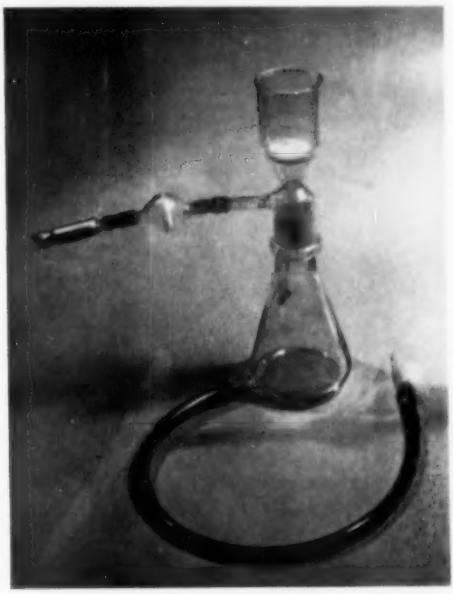

Fig. 1.—Fritted glass filter assembly.

were cultured in Brewer's liquid thioglycollate medium. With the exception of antibiotic solutions, solutions in oil, and carbachol solutions, all collyria contained chlorobutanol 0.5% as a preservative. Carbachol bottles contained benzalkonium 1:3,000, as recommended by O'Brien and Swan.[19]

The results of the survey were impressive in that the contents of 575 out of 576 bottles were found to be sterile. The one contaminated solution was 1.5% carbachol in benzalkonium chloride 1:3,000; this yielded an abundant growth of a pigment-producing strain of Ps. aeruginosa on starch agar and in broth. Twenty-seven opened bottles of fluorescein were among the sterile solutions.

The case of fluorescein requires special consideration. As was originally noted by McCulloch,[20] solutions of this substance appear to be both highly susceptible to contamination and highly resistant to sterilization by added preservatives. In testing fluorescein samples from 50 different sources in the San Francisco Bay area,

Vaughan [3] found two instances of contamination in solutions containing chlorobutanol. Neither of these was due to Pseudomonas. A similar survey by Theodore [21] in New York City showed 100% Pseudomonas contamination of fluorescein solutions from the offices of ophthalmologists. To the best of our knowledge, based on periodic surveys and spot checks, no instance of Pseudomonas contamination of fluorescein solutions has been reported in our hospital during the past 20 years. One instance of contaminated homatropine solution prepared in our pharmacy occurred in an ophthalmologist's office. The solution in question was believed to have been opened as long as a year previously and was in a dropper bottle intended for use by an individual patient. The low incidence of contamination in our clinic is attributed to the careful technique of preparation and use, as well as to the bacteriostatic properties of chlorobutanol.

Chlorobutanol 0.5% was first introduced into all collyria used or dispensed at the Massachusetts Eye and Ear Infirmary in 1926, and has been in continuous use since that time. Collyria containing it have been repeatedly instilled into the anterior chamber at the time of intraocular surgery, without any instance of endothelial damage or other ill effects upon the tissues within the eye. It has been used in miotics for many years by hundreds of glaucoma patients without a single instance of sensitization being specifically attributed to it. Although it has been widely used as a preservative for injectible substances, it is not to be found in an extensive listing of drugs implicated at any time as a cause of allergic or hypersensitive reactions.[22] On the other hand, mercurials as a group are listed as causative of contact dermatitis and other adverse effects. The advantage of being remarkably innocuous rests clearly on the side of chlorobutanol.

The pharmacologic activity of other ingredients of ophthalmic collyria is not impaired by the presence of chlorobutanol.

The chemical stability of chlorobutanol in the pH range recommended by us for alkaloidal solutions has been demonstrated. A tendency to slow evaporation of chlorobutanol can be prevented by the use of rubber sealers in bottle caps. Since water likewise evaporates at a significant rate through cardboard sealers, the use of rubber sealers is highly desirable for this reason alone.

The use of 7.5 cc. collyrium bottles is recommended as a means of reducing evaporation and likelihood of contamination.

Mechanisms of contamination of eye solutions have recently been reviewed by King,[2] who stresses the importance of careful technique and offers many practical suggestions deserving of adoption. The use of individual sterile droppers is recommended by him, as well as by Thygeson [23] and Hogan.[24] This system was put into effect in our hospital about 1925. At first, droppers were collected after use and resterilized by boiling. For the past four years autoclaved glass droppers have been permanently discarded after a single introduction into collyria. We are currently experimenting with ethylene oxide sterilization of disposable plastic droppers of the soda-straw type. It is our conviction that the old-fashioned community dropper bottle should be banished from the clinic, office, hospital ward, and operating room forever. For individual medications dispensed to patients, the technique of sterilization here outlined, combined with the use of chlorobutanol as a preservative, offers a reasonable guarantee of sterility. For commercially prepared solutions, the introduction of the plastic dispensing container appears to be an advance in the right direction, provided it is to be used by only one patient.

Irrigation of the conjunctival sac, especially in the presence of a corneal abrasion, must be performed with a solution of known sterility. Hind and Szekely [25]

rightly emphasize the possibility of contamination of saline solutions. Our answer to this problem has been not the addition of a chemical preservative but the adoption of autoclaved individual units (Fig. 2). Rubber syringes, autoclaved and handled with sterile transfer forceps, are used for the actual irrigation.

Whatever system is adopted, the vagaries of bacterial growth and the fallibility of human endeavors make it imperative to determine periodically the effectiveness of preventive measures in force. The practice of culturing solutions and ointments in active use should not be limited to occasional surveys or to sporadic efforts occasioned by the outbreak of infection. An ophthalmologist guilty of using medications of unproved sterility in the presence of a corneal epithelial defect is liable to the gravest censure, not to mention litigation for malpractice. The habit of allowing a few drops of the collyrium to fall into a culture tube or onto an agar plate, repeated

Fig. 2.—Sterile saline irrigation set for individual use.

at regular intervals, provides a periodic check on sterility. Employed on a large scale, it could exert a favorable influence on morbidity statistics.

SUMMARY AND CONCLUSIONS

Solutions of ophthalmic drugs should be accurately prepared and dispensed in a sterile state.

Unbuffered solutions of the principal ophthalmic alkaloids withstand autoclaving under the proper conditions.

Tests of the antibacterial properties of four substances recommended as preservatives for collyria showed that none was uniformly bactericidal.

Chlorobutanol 0.5% is recommended as most nearly fulfilling the requirements for the ideal preservative for ophthalmic solutions.

A practical method is outlined for preparing and sterilizing collyria in smaller pharmacies.

The effectiveness of measures employed in a large eye hospital is reviewed on the basis of clinical experience over a period of 29 years.

The importance of careful technique in office and hospital practice is stressed, with special emphasis on the use of individual sterile droppers for administering medications.

Dr. David G. Cogan gave helpful criticism in this study. Miss Thelma Lezberg, Mrs. Lillian Spongberg, and Mrs. Mary Pedulla gave technical assistance.

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HISTOLOGIC DEMONSTRATION OF HEAT INJURY TO COLLAGEN TISSUES OF THE EYE

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WHEN REDUCED to its simplest terms, repair of retinal detachment requires that the retina be brought into apposition with the pigment epithelium and choroid and fixed by surgically induced chorioretinal scar. The surgical procedure is formulated on the premise that proliferation of connective tissue occurs in the reparative phase of reaction to physical injury. For successful application of this premise, injury must be induced in the choroid and adjacent tissues at selected sites and depths without excessive destruction. Most contemporary operative techniques rely on heat generated by diathermy for induction of the desired injury, but even the most satisfactory results are not obtained without some undesirable destruction of the sclera. Despite the wide acceptance of this technique with its undesirable side-effects, there are few published experimental data on the factors which determine the intensity and spread of diathermy heat in the ocular tissues. Histopathological tissue study is a logical method of investigation, but staining techniques for demonstrating heat injury to the ocular tissues have not been wholly satisfactory. It is our purpose to report a method which more sharply demarcates heat-induced changes in the sclera than any used previously. It is a modification of the Ross and Walker [1] method of demonstrating heat alterations in collagenous tissue.

Ross and Walker noted that when paraffin sections of normal and heat-altered collagen of a rat's tail were stained for 24 hours at room temperature by an aqueous solution of aniline blue and phosphomolybdic acid, both the normal and the heat-altered collagen appeared blue. Orange G added to this aqueous solution served only as a cytoplasmic and keratin stain; however, when aniline blue and phosphomolybdic acid were dissolved in absolute alcohol rather than water, there was a striking difference in staining properties of normal and heat-altered collagen with orange G. Normal collagen stained blue with the aniline blue, in contrast to the thermally altered collagen, which stained intensely with the orange G. By staining duplicate sections, they found that the dye uptake of normal and heat-altered collagen was mutually exclusive; i. e., normal collagen would not stain with orange G, and burned collagen would not stain with aniline blue. From this and other observations, Ross and Walker deduced that some component of the dermal collagen was rendered water-soluble by the heat, so altering its staining characteristics that aniline blue was rejected.

This anhydrous technique permitted the detection of alterations in dermal collagen structures by temperatures as low as 70 to 80 C. Because of this sensitivity

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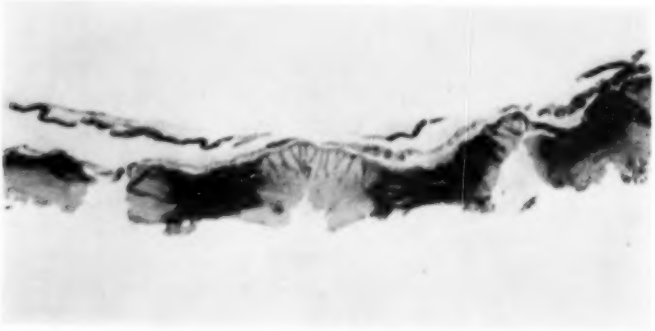
and excellent differential staining qualities, we felt that the method could be adapted for microscopic study of scleral burns sustained from diathermy in retinal detachment surgery. For proper investigation of this possibility we had to use human eyes that were to be enucleated for other purposes. By this method diathermy was applied on viable tissue under conditions simulating retinal detachment surgery. The sclera was exposed during enucleation, and the desired type of diathermy was applied. In some eyes aqueous was withdrawn from the anterior chamber to permit heat shrinkage to occur. The type of diathermy current, the amperage, and the electrodes used were catalogued, and any immediate effect on the globe (i. e., shrinkage) was noted. The globes were enucleated and placed in a modified Carnoy's fixative for only four hours.* A longer period in the fixative was found to cause undesirable distortion of the specimen.

After removal from the fixative, the globes were studied under a dissecting microscope. Calottes were cut from the areas where diathermy had been applied. The globes were placed in alcohol for standard processing, but the calottes were immersed



Section of sclera and choroid showing multiple perforations following application of diathermy. The orange-colored sclera represents heat-altered collagen, and the blue-staining sclera is unaffected.

in two changes of 95% ethyl alcohol of one hour each. They were placed in dioxane for 12 to 24 hours and embedded in paraffin. Sections were made and stained overnight in the following anhydrous modification of Mallory's collagen stain:

Aniline blue	1.0 gm.
Orange G	2.0 gm.
Phosphomolybdic acid	2.0 gm.
Absolute methyl alcohol	200 cc.

The stained sections were rinsed twice in absolute isopropyl alcohol, cleared in xylene, and mounted in balsam.

As shown in the accompanying Figure, the thermally treated portion of the sclera stained brilliantly with orange G. The heat-altered collagen of the sclera thereby was clearly demarcated from the normal collagen. Other stains of these sections, including hematoxylin and eosin and the standard Mallory trichrome stain,

* Carnoy's fixative is made by adding 30 cc. of chloroform and 10 cc. of glacial acetic acid to 60 cc. of absolute ethyl alcohol. In our fixative 95% ethyl alcohol was substituted for absolute alcohol.

were inferior in this respect. Of interest was a difference in the staining characteristics of the various levels of the normal sclera and cornea. The inner aspect of these tissues stained with orange G, suggesting that a water-insoluble fraction normally is present in the collagen of this level. The new technique did not clearly demarcate between the affected and the nonaffected areas of choroid, retina, and vitreous.

As a general all-purpose fixative for enucleated eyes, Carnoy's solution was found to be unsatisfactory because it dehydrated the globe excessively. When globes were maintained in solution for 24 hours, they collapsed and became markedly distorted. They could not be restored completely by insufflation with alcohol. In addition, the outer coats became excessively rigid and discolored. The cornea became opaque, making gross examination of the anterior chamber impossible. The vitreous also became quite cloudy, making gross examination of the retina, optic disc, lens, and fundus unsatisfactory. In one instance a retinoblastoma was reduced to an amorphous mass with a cheesy consistency; however, despite the gross distortion, celloidin sections of these specimens had satisfactory cellular detail, as compared with globes fixed in formalin or Zenker's solution.

SUMMARY

The improved histologic method of demonstrating heat injury to collagenous tissue described by Ross and Walker was modified and adapted for study of the changes induced in the globe of diathermy in retinal detachment surgery. Preliminary studies indicate that the method is superior to previously used techniques for study of scleral burns. It is not suitable for routine histologic study of the globe because it causes gross distortion of the tissues.

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ELEVATED LESIONS OF THE MACULAR AREA

A Histopathologic Study Emphasizing Lesions Similar to Disciform Degeneration of the Macula

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DIFFICULTIES encountered in the differential diagnosis, in the eyes of two patients, of almost identical unilateral elevated macular lesions, one benign, the other malignant, provided the stimulus for this paper. Both eyes were enucleated, with a clinical diagnosis of malignant melanoma of the macula. Because one proved to be a disciform degeneration with an unusual degree of elevation, a study of non-neoplastic lesions of the macula was undertaken with the hope of gaining information which might help to avoid such errors in the future. Permission was obtained from the Armed Forces Institute of Pathology to study sections of 23 eyes coded as disciform degeneration of the macula in the Registry of Ophthalmic Pathology.

The differential diagnosis of macular lesions producing elevation is primarily concerned with malignant melanoma and senile disciform degeneration of the macula. Other lesions which occur considerably less frequently include (1) choroidal or subretinal hemorrhage, (2) metastatic carcinoma, (3) hemangioma of the choroid, (4) tuberculoma of the choroid, (5) exudative retinitis of Coats, and (6) nonspecific hyperplasia of the pigment epithelium following injury or inflammation.

The difficulty in clinical differentiation of malignant melanoma and senile disciform degeneration of the macula is emphasized in the literature by the number of eyes with a lesion proving to be disciform degeneration that were removed because of a clinical diagnosis of malignant melanoma. Verhoeff and Grossman [1] and Duke-Elder [2] have listed several clinical observations which contribute to diagnostic accuracy. They urge that enucleation be delayed in cases in which the size and situation of the lesion, the texture of the retina over the surface of the lesion, the absence of inflammation, the absence of extensive retinal separation, the existence of circinate retinitis, and the presence of subretinal hemorrhagic extravasations adjacent to the mass suggest a diagnosis of disciform degeneration. Reese * has emphasized the fact that in disciform degeneration macular or vascular changes are frequently found in the opposite eye and serve as useful clues. He also states that disciform degeneration may grossly resemble malignant melanoma because of the dark color imparted by its high hemosiderin content. Bedell [4] utilized serial observations of lesions by fundus photography to detect signs of increasing size. He also considered choroidal or retinal arteriosclerosis as important signs in the diagnosis of disciform degeneration. Radioactive phosphorus uptake studies may, in

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* Reese,[3] p. 276.

the future, be of help in the differentiation of lesions of the posterior pole of the eye. At the present time, a satisfactory counter for such lesions is not available, although the method has been used successfully in lesions of the anterior segment of the globe.

In younger persons juvenile disciform degeneration of the macula, which is similar in appearance to senile disciform degeneration, may occasionally simulate a tumor. It is more frequently, however, accompanied by ophthalmoscopically visible retinal or choroidal hemorrhages. Recent clinical observations suggest that many of the lesions called juvenile disciform degeneration are in reality central choroiditis.† Careful search of the peripheral fundus in such eyes often reveals areas of choroiditis elsewhere. The material available for this paper included only lesions similar to the senile type.

Relatively few histopathologic reports of senile disciform degeneration have been made. A careful analysis of the literature by Verhoeff and Grossman [1] in 1937 revealed only 13 acceptable cases, to which they added 2 of their own. Since the appearance of their paper, records of only eight additional eyes could be found.‡ This brings the total of histologically studied eyes to 23.

Pagenstecher and Genth § are credited with the first of these reports, in 1875. Following their original paper, occasional cases appeared in the literature under various names. These have been tabulated by Adler [14] and include such terms as "senile macular exudative retinitis," "disciform degeneration of the macula," "chorioretinitis centralis," "fibroma or fibrochondroma of the macula," "pseudotumor of the macula," "retinitis exudativa externa with bone formation in the macula," "senile form of retinitis exudativa (Coats's disease)," "senile changes in the macula due to arteriosclerosis," and "subretinal exudates simulating sarcoma of the choroid." In the now classic report of Junius and Kuhnt [15] in 1926, the condition was established as a clinical entity, and since that time the term "senile disciform degeneration of the macula" has received the widest acceptance.

The characteristic lesion of disciform degeneration in its late stages consists of a mound of connective tissue and proliferated pigment epithelial cells located beneath the retina in the macular region. There is usually vascularization of the outer portion of the mass as a result of proliferation of small vessels through breaks in the lamina vitrea (Bruch's membrane). Areas of hemorrhage and chronic inflammatory cells are sometimes found within the lesion.

The origin of the connective tissue mass is obscure, because most of the eyes reported have been enucleated at a late stage of the disease. Michel,[16] in 1878, suggested that the connective tissue mound was the result of organization of a chorioretinitic exudate. A transudation of fluid from the choriocapillaris into the subretinal space, with subsequent organization, was thought by Behr [17] to be the result of a senile change in Bruch's membrane. A significant contribution was made by Verhoeff and Grossman, who demonstrated in two eyes that the mass of connective tissue was the result of organization of hemorrhage occurring between the lamina vitrea and the layer of pigment epithelium. They regarded the hemorrhage as the result of some disturbance, possibly temporary, in the choroid and suggested that it reached the subretinal space through tears in the lamina vitrea. When no such

† Adler, F. H.: Personal communication to the author.

‡ References 5 to 12.

§ Pagenstecher and Genth,[18] cited by Junius and Kuhnt.[15]

tears were found, they postulated a seepage of blood through an intact lamina vitrea. Connective tissue cells participating in organization of the hemorrhage were thought to be primarily of choroidal origin. Magitot,[9] in 1939, and Holm,[11] in 1941, postulated a primary disorder of pigment epithelium, possibly as a result of malnutrition by an inadequate choriocapillaris. They contended that this disorder resulted in secretion of an albuminous fluid by pigment epithelial cells. Replacement of the fluid by connective tissue was mediated by fibroblasts arising by metaplasia from these same pigment epithelial cells.

Klien [18] has demonstrated that a disciform connective tissue lesion of the macula may develop after a subretinal hemorrhage due to sclerosis of perimacular and retinal capillaries and precapillaries. The same changes in such patients may result in a circinate retinopathy. She believes that organization of the hemorrhage

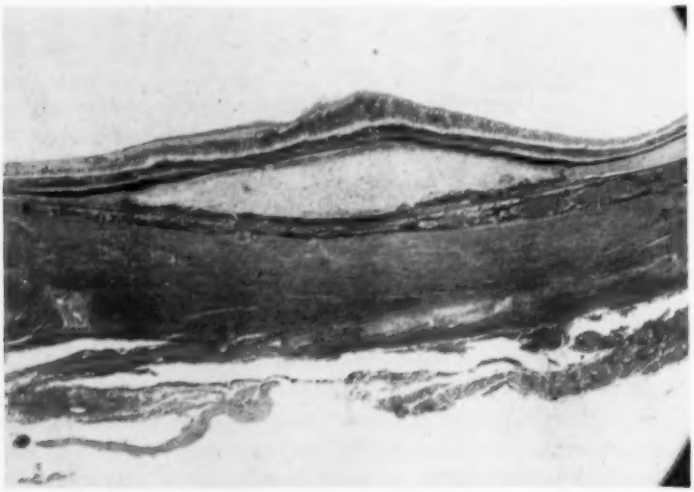

Fig. 1 (Specimen 1; T.B.).—Low-power view of the macular lesion, showing division of the connective tissue mound by the layer of pigment epithelium. Serous detachment of the retina is beginning at the edge of the lesion. × 16.

in the macula is primarily from retinal sources, although sclerosis of choroidal vessels, hemorrhage, and organization through breaks in the lamina vitrea may occur simultaneously with the retinal changes.

The fairly frequent occurrence of the disciform type of macular lesion in cases of angioid streaks has also attracted some attention. Verhoeff and Grossman were of the opinion that choroidal hemorrhages, commonly seen in the presence of angioid streaks, were indicative of vascular disturbances in the choriocapillaris and that a macular hemorrhage with organization might be a logical result.

HISTOPATHOLOGIC STUDY

Specimen 1.—T. B., a 68-year-old white man, was first seen by Dr. Harold G. Scheie on May 23, 1952, complaining of distorted vision in the left eye since about Jan. 1, 1952. Vision had become markedly impaired about May 1, 1952. His visual acuity was correctible to 6/7.5 O.D. and to counting fingers at 1 ft. (30 cm.) O.S.

External examination was negative except that the left pupil was slightly larger than the right. The anterior segments appeared normal by slit-lamp examination. Ophthalmoscopic examination of the right eye was negative. In the left eye, the media were clear, and the disc appeared healthy. A large, smooth, pale-gray, elevated lesion with indistinct borders was found in the macula. The vessels on the surface of this lesion could be seen most clearly with a + 6.00 D. lens. There was no evidence of retinal or choroidal arteriosclerosis. Two small white exudative areas could be seen just temporal to the mass, but there were no visible hemorrhages. Visual fields revealed a large central scotoma, breaking through to the periphery above.

The patient was seen again on July 25, 1952, at which time the macular lesion appeared larger and the vessels on its surface could be seen most clearly with a + 8.00 D. lens. Visual fields were unchanged. Enucleation was advised because of the possibility of a malignant melanoma. The patient was therefore admitted to the hospital, where a general physical examination, laboratory studies, and x-rays of the chest and long bones were all negative. The left eye was enucleated on Aug. 7.

The eye was fixed in a buffered solution of 10% formalin, embedded in nitrocellulose, sectioned, and stained with hematoxylin and eosin.

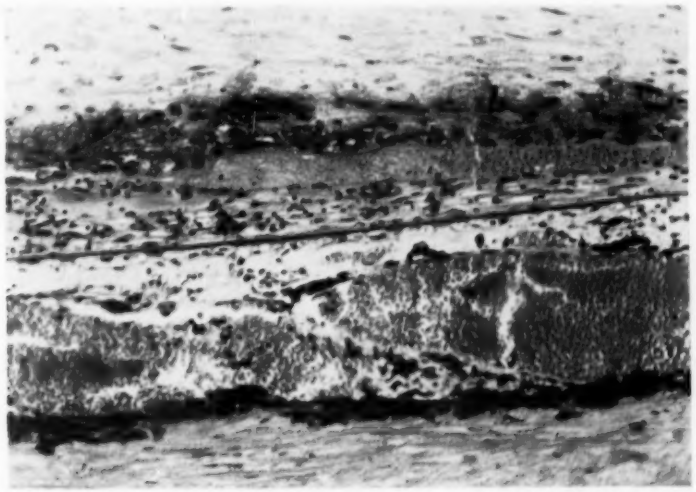

Fig. 2 (Specimen 1; T.B.).—Division of the mound into two layers by proliferated pigment epithelium and a layer of blood and fibrin. There is some irregularity of the lamina vitrea. × 188.

Gross Examination.—The globe measured 23 by 23 by 24 mm. A round corneal button had been removed for use in a corneal transplant operation. The eye was sectioned in a horizontal plane, and, except for the macular region, it was grossly normal. In the macular region was a smooth 2 mm. elevation of the retina without evidence of retinal hemorrhages. Section through the lesion revealed a dense, grayish subretinal mass of tissue closely adherent to the choroid. Because a tumor was suspected, a small portion of this mass was removed for paraffin embedding and early diagnosis.

Microscopic Examination.—The anterior segment of the eye was normal, except for the absence of the central portion of the cornea. A large mound of connective tissue was present in the macular region between the retina and the lamina vitrea. This mound was roughly divided into two layers, separated by an irregular band of pigment epithelial cells (Fig. 1). In the much thinner portion of the mass external to the pigmented cells, the connective tissue was highly cellular, vascularized, and in some sections infiltrated by lymphocytes. In some of the sections a layer of fibrin and red blood cells was found within this vascular portion and adjacent to the pigment epithelium (Fig. 2). The inner, much thicker portion of the mound was composed of avascular hyaline connective tissue, in which were found several areas of recent hemorrhage.

The pigment epithelial cells separating the two connective tissue layers were arranged roughly in a double row, with many intercommunicating bridges. In some areas they were grouped around

Fig. 3 (Specimen 1; T.B.).—Break in the lamina vitrea with a large vessel passing through it into the connective tissue mound. A deeply staining fibrinoid material is trapped between the layers of pigment epithelium. Cells resembling pigmented fibroblasts are seen above the layer of pigment epithelium. × 188.

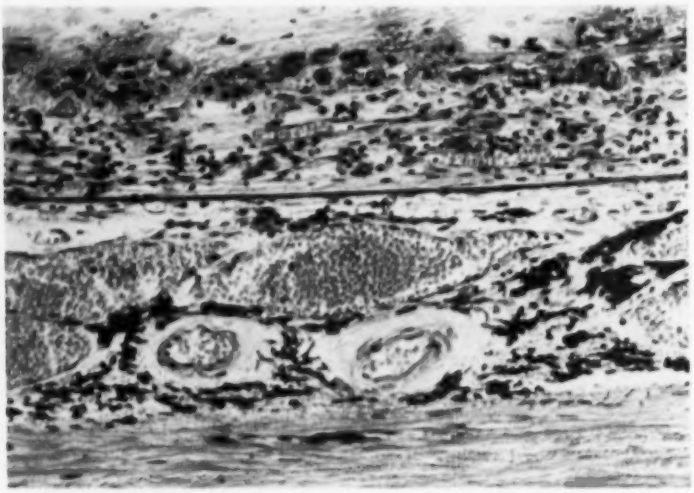

Fig. 4 (Specimen 1; T.B.).—Arteriosclerosis of two large choroidal vessels. Note the vascularity of the outer portion of the connective tissue mound. × 218.

small clumps of a deeply staining eosinophilic and amorphous material, resembling fibrin (Fig. 3). This material took an orange color with a Mallory trichrome stain and with a Van Gieson connective tissue stain, suggesting that it was either fibrin or a closely related product of the breakdown of blood protein. In other areas young connective tissue cells were found between the rows of pigment epithelium. The epithelial cells themselves were swollen and irregular. A few had assumed a fusiform shape, with fibrils extending into the connective tissue mass, so that they resembled pigmented fibroblasts (Fig. 3). Stains for iron revealed small amounts of free iron in the connective tissue adjacent to the lamina vitrea. The lamina vitrea was irregularly thickened, and its continuity was broken in several of the sections. Some of these breaks permitted passage of large or small blood vessels between the choroid and the connective tissue mound (Fig. 3). Smaller breaks in the lamina vitrea contained only a few fibroblastic cells.

There was moderate arteriosclerosis of the larger vessels in the posterior portion of the choroid (Fig. 4). In the macular area there was marked hyaline thickening of the vessels of the choriocapillaris and of the medium-sized vessels of the choroid (Fig. 5). Sections stained with Van Gieson's connective tissue stain most clearly demonstrated the extent of the sclerosis in this area. On either side of the connective tissue mound, and over its surface, the retina was

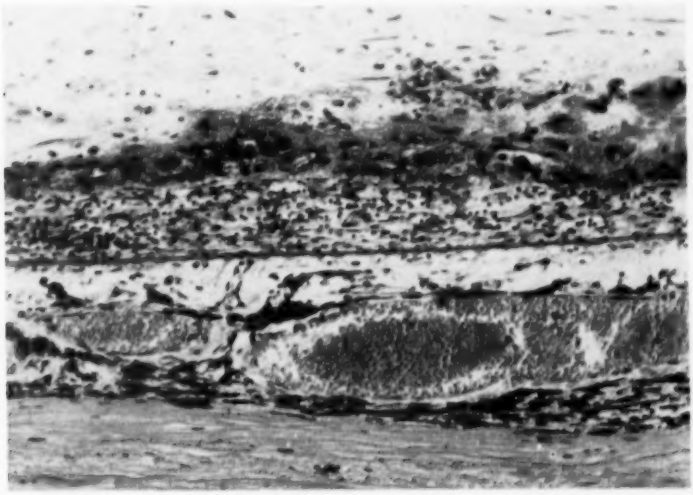

Fig. 5 (Specimen 1; T.B.).—Arteriosclerosis of the choriocapillaris and of medium-sized vessels of the choroid. There is moderate lymphocytic infiltration of the macular lesion. × 155.

lifted by a layer of serous fluid. This layer of fluid may have accounted for the much larger clinical appearance of the mass. The retina over the macular lesion showed remarkably little change, and even the layer of rods and cones was intact in most areas. There were a few small cystic areas in the layer of ganglion cells and in the inner nuclear layer.

SPECIMENS 2 through 24.—These specimens were all obtained from the Registry of Ophthalmic Pathology and were coded as disciform degeneration. The histopathologic findings are summarized in Tables 1 and 2.

COMMENT

Thirteen of the eyes were enucleated because of a mistaken diagnosis of malignant melanoma (Table 1). Histologically the lesions in seven resembled those in previously reported cases of senile disciform degeneration of the macula. These eyes showed a typical mound of connective tissue and proliferated pigment epithelium. In three other eyes the macular elevation was the result of recent subretinal hemorrhages with partial organization. Two showed minimal proliferation of the pigment epithelium and connective tissue in the macula, and the 13th eye showed

an elevated connective tissue mass in the macula associated with numerous chorioretinal scars elsewhere in the eye, probably the sequela of inflammation.

Careful examination of all available sections revealed small subretinal or retinal hemorrhages in 7 of the 13 eyes. Serous separation of the retina, of variable degree, was present in only four. While all the lesions studied were in the area bounded by

TABLE 1.—*Eyes Enucleated Because of Suspected Malignant Melanoma*

Specimen No.	Clinical Diagnosis	Age, Yr.	Histologic Cause of Macular Elevation	Associated Histologic Findings			
				Retinal or Subretinal Hemorrhage	Serous Retinal Detachment	Choroidal Sclerosis	Breaks in the Lamina Vitrea
Specimen 1 (T. B.)	Malignant melanoma; increasing size, no hemorrhages	68	Connective tissue mound	—	+	+	+
Specimen 2 (AFIP acc. 84365)	Malignant melanoma; hemorrhages around lesion	78	Connective tissue mound	+	+	—	
Specimen 3 (AFIP acc. 120292)	Malignant melanoma; no hemorrhages	65	Connective tissue mound	—	—	—	+
Specimen 4 (AFIP acc. 302819)	Malignant melanoma; no hemorrhages, macular lesion increasing in size	81	Connective tissue mound	+	—	+	+
Specimen 5 (AFIP acc. 578097)	Malignant melanoma; central elevated mass, extensive serous detachment, no hemorrhages, severe hypertension	..	Connective tissue mound	—	+	—	—
Specimen 6 (AFIP acc. 283077)	Malignant melanoma; no hemorrhages, central elevated mass	57	Connective tissue mound	—	+	—	—
Specimen 7 (AFIP acc. 593466)	Malignant melanoma; no hemorrhages	57	Connective tissue mound	—	—	—	—
Specimen 8 (AFIP acc. 265782)	Malignant melanoma; large eccentric mass, hemorrhage over surface	77	Subretinal hemorrhage; intraretinal hemorrhage	+	—	—	—
Specimen 9 (AFIP acc. 541939)	Malignant melanoma; small pigmented spot adjacent to macula; x-ray therapy; vitreous hemorrhage, retinal detachment	68	Large subretinal hemorrhage with early organization; intraretinal hemorrhage	+	—	—	+
Specimen 10 (AFIP acc. 60731)	Malignant melanoma; no hemorrhage, no history of injury	11	Subretinal hemorrhage; mass of organized tissue centrally	+	—	—	—
Specimen 11 (AFIP acc. 541948)	Malignant melanoma; chorioretinitis, diffuse and central, no hemorrhages	45	Connective tissue mound; many chorioretinal scars	+	—	—	—
Specimen 12 (AFIP acc. 316969)	Malignant melanoma; pigmented lesion above macula, increasing in size, no hemorrhages	54	Pigment epithelial proliferation; thin connective tissue plaque	—	—	—	—
Specimen 13 (AFIP acc. 332136)	Malignant melanoma; elevated extramacular mass, increasing size, no hemorrhages mentioned	41	Pigment epithelial proliferation; thin connective tissue plaque	+	—	+	+

the superior and inferior temporal vessels, not all of them were centrally located. Four of the lesions were almost entirely eccentric, and several others partially covered the fovea but may have been centered eccentrically. Mechanical distortion of the retina and destruction of its outer layers were found in all but one of the specimens. Only 3 of the 13 eyes showed histologic evidence of severe choroidal arteriosclerosis. Further study of the choriocapillaris, however, and utilization of special stains might well have indicated a higher incidence of sclerosis. Retinal arteriosclerosis was recognizable in significant degree in only one eye.

The second group of cases (Table 2) includes 11 in which no clinical diagnosis of a macular lesion had been made and in which macular lesions were an incidental finding after enucleation. All but one of the eyes were removed because of pain and loss of vision associated with intractable glaucoma. Seven of them contained mounds of connective tissue and proliferated pigment epithelium, histologically identical to the lesions of Group I, which were thought to be lesions of disciform degeneration. It seemed unlikely that the lesions were related to the disease for which enucleation was performed. Although the eyes of Group II had not been removed because of a problem in differential diagnosis, they are included in this

TABLE 2.—*Eyes Enucleated for Reasons Other Than Suspected Malignant Melanoma*

				Associated Histologic Findings			
Specimen No.	Clinical Diagnosis	Age, Yr.	Histologic Cause of Macular Elevation	Retinal or Subretinal Hemorrhage	Serous Retinal Detachment	Choroidal Sclerosis	Breaks in the Lamina Vitrea
Specimen 14 (AFIP acc. 181601)	Glaucoma secondary to intumescent lens	84	Connective tissue mound	—	—	+	+
Specimen 15 (AFIP acc. 270074)	Absolute glaucoma; macular lesion described 2 yr. previously; probable metastatic tumor	79	Connective tissue mound	—	—	—	+
Specimen 16 (AFIP acc. 149371)	Chronic glaucoma; secondary corneal ulcer	75	Connective tissue mound	+	—	—	—
Specimen 17 (AFIP acc. 183551)	Corneal ulcer; endophthalmitis; secondary glaucoma	77	Connective tissue mound	+	—	+	+
Specimen 18 (AFIP acc. 490222)	Autopsy; multiple retinal hemorrhages six days after cataract operation	72	Connective tissue mound; subretinal hemorrhage	+	—	+	+
Specimen 19 (AFIP acc. 602790)	Secondary glaucoma; anterior staphyloma; no macular lesion described	75	Connective tissue mound; retinal arteriosclerosis	—	—	—	—
Specimen 20 (AFIP acc. 191956)	Secondary glaucoma; trauma several years previously	56	Connective tissue mound	—	—	—	+
Specimen 21 (AFIP acc. 197247)	Secondary glaucoma; injury 1 yr. previously	9	Minimal proliferation of pigment epithelium	—	—	—	—
Specimen 22 (AFIP acc. 122745)	Secondary glaucoma; recurrent inflammation since childhood	52	Minimal proliferation of pigment epithelium	—	—	—	—
Specimen 23 (AFIP acc. 155384)	Absolute glaucoma; no macular lesion described	75	Small connective tissue mound; diffuse uveitis	—	—	—	—
Specimen 24 (AFIP acc. 269959)	Absolute glaucoma	80	Minimal proliferation of pigment epithelium and connective tissue	—	—	—	—

report for the additional information which they contribute to the present study of elevated macular lesions.

Of the seven eyes in Group II which contained lesions resembling disciform degeneration, hemorrhages which might have been detected clinically were present in only three. None of the seven showed extensive serous retinal separation, and three of them showed definite sclerosis of choroidal vessels. The remaining four eyes showed histologically only a minimal degree of proliferation of pigment epithelium in the macula. Although they did not demonstrate the typical picture of a fully developed senile disciform degeneration, they may represent an earlier phase of the same reaction.

All eyes were studied for evidence leading to an understanding of their histogenesis. With the exception of Specimen 1, only a few sections were available from

each eye. Serial sections, and in some cases special stains, would be necessary for accurate analysis of the various stages in the pathogenesis of these lesions. Nevertheless, it was possible, particularly from the study of Specimen 1, to make certain observations which seem to be of value. There is evidence confirming the impression of Verhoeff and Grossman that in some instances the lesion of disciform degeneration is the result of an organized hemorrhage. The presence of iron within the lesion in Specimen 1 is supportive evidence in favor of such an origin. A substance was found in several of the lesions which, as a result of differential staining, was thought to be fibrin or some closely related fraction of blood protein. It is suggested from the study of these eyes that phagocytosis and organization of this material by pigment epithelial cells is an important phase in the pathogenesis of disciform degeneration of the macula.

Holm and Klien have indicated that connective tissue arises from more than one source. Findings in this study seem to confirm this belief. In most instances, a form of hyaline connective tissue appears to be the result of metaplasia of pigment epithelial cells, while vascular connective tissue or granulation tissue outside the layer of pigment epithelium may be the result of organization from choroidal sources through breaks in the lamina vitrea.

Examination of all eyes in both groups indicates that inflammation, or hemorrhage resulting from trauma, may result in a lesion, the end-stage of which is identical with that of disciform degeneration. The formation of a subretinal connective tissue may, in certain instances, be a nonspecific response by the pigment epithelium to a variety of stimuli.

An attempt was made to correlate the histologic and clinical findings of this study to determine their value in the differential diagnosis of benign elevated lesions of the macula and malignant melanoma. Reese || has stated that clinically visible hemorrhagic extravasations are sometimes seen in malignant melanoma, but are not routinely present. The frequent occurrence of retinal and subretinal hemorrhages in the eyes with benign macular lesions studied histologically confirms the contention of others that clinical evidence of such extravasations is of diagnostic value. It is apparent, however, that grossly visible hemorrhages are not a universal finding in disciform degeneration of the macula.

The rarity of extensive serous detachment in the group of eyes included in this study is in keeping with the impression of previous authors. This is in distinct contrast to the common occurrence of serous retinal detachment associated with malignant melanoma.

The study indicates that disciform degeneration and other benign macular lesions are not always centered in the fovea. Clinical evidence of an eccentrically located mass, therefore, could indicate either a tumor or a benign lesion, and the fact that it is eccentric would not be of especial differential diagnostic value.

Gradual increase in the size of a macular lesion is frequently considered a suggestive sign of tumor, while disciform degeneration classically decreases in size as organization progresses. Five of the 13 eyes in Group I, however, gave clinical evidence of enlarging central lesions. Secondary hemorrhage within the lesion, or the accumulation of serous fluid over its surface, may account for gradual increase in the size of benign macular lesions.

|| Reese,[3] p. 257.

Reese ¶ has observed that the retina over the surface of a proliferative type of senile macular degeneration is less uniform in appearance than the retina over the surface of a malignant melanoma. He notes, however, that in malignant melanoma the retina sometimes becomes adherent to the tumor and appears heavily pigmented, due to replacement of retinal elements by proliferating pigment epithelium. The results of the present study indicate almost universal secondary destructive changes in the retina associated with disciform degeneration. Pigment, however, is deeply buried in connective tissue in such cases, and is less likely to be visible ophthalmoscopically. The striking lack of retinal change in the one eye which I observed (Specimen 1) suggests that the retina may occasionally present a uniform appearance clinically, making it difficult to differentiate from a malignant melanoma.

The infrequent occurrence of histologically recognizable choroidal or retinal arteriosclerosis in this series of eyes has been noted. Clinical observations indicating the presence or absence of such vascular changes would appear to be of little help in the differential diagnosis of elevated macular lesions.

CONCLUSIONS AND SUMMARY

A review of the literature on senile disciform degeneration of the macula and its differential diagnosis has been made. A histologic study has been made of 24 eyes with non-neoplastic central elevated lesions resembling disciform degeneration, 23 of which were from the Registry of Ophthalmic Pathology. The study indicates that disciform degeneration may frequently be the result of spontaneous hemorrhage, as suggested by Verhoeff and Grossman, but that entirely similar lesions may also be the result of inflammation or of trauma. The clinical differentiation of disciform degeneration of the macula and malignant melanoma is often difficult. The histologic study indicates that hemorrhagic extravasations adjacent to the lesion, the absence of serous retinal detachment, and the absence of pigment changes over the surface of the lesion are valuable clinical signs favoring a diagnosis of disciform degeneration. Progressive enlargement of the lesion and eccentric location of the lesion are signs compatible with the diagnosis of either disciform degeneration or malignant melanoma. It would seem that removal of an eye for a suspected malignant melanoma which later proves to be a disciform degeneration of the macula is occasionally unavoidable with present diagnostic techniques.

¶ Reese,[3] p. 250.

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LIPOLIQUID IN TREATMENT OF HEMORRHAGIC DIABETIC RETINOPATHY

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MANY DRUGS have been used in an attempt to abort the vascular complications of diabetes mellitus. To date none has proved effective. Recently the liver has been implicated as possibly playing a role in these vascular complications. A tendency toward fatty infiltration of the liver has been noted in diabetes and arteriosclerosis. This fatty infiltration is believed to impair liver function and thereby predispose, in some as yet unknown manner, to increased vascular disease. By reducing fatty infiltration by the use of lipotropic substances, and thereby improving liver function, it is hoped that the vascular disease will be arrested. The lipoliquid used in this study contains choline, the most effective lipotropic agent known, inositol, and vitamin B_{12}, believed to be catalysts in the formation of the mobile choline-based phospholipids.

It is the purpose of this report to note the effect of Lipoliquid used in the treatment of 50 consecutive cases of diabetic retinopathy from the metabolic clinic of the Mount Sinai Hospital over a period of two years. The total daily dose amounted to 11.25 gm. of choline, 12.6 γ of vitamin B_{12}, and 225 mg. of inositol.

All the patients were between the ages of 55 and 75, with a known duration of diabetes of between 15 and 25 years. One-third of the cases were of mild, one-third of moderately severe, and one-third of severe diabetes, as judged on the basis of insulin requirements.

Of the 50 cases, 35 showed varying degrees of diabetic retinopathy without retinitis proliferans. Visual acuity in this group ranged from 20/50 to 20/100. With Lipoliquid therapy many of the hemorrhages were noted to resorb within a period of three weeks. No change was noted in the status of the microaneurysms or exudates. Despite Lipoliquid therapy, recurrent hemorrhages occurred in all cases. At the end of the two-year period of observation 15 of the cases in this group had maintained their original visual acuity, while the other 20 had lost between one-half to two lines. Two of the cases show evidence of mild retinitis proliferans.

Fifteen of the 50 cases showed diabetic retinopathy plus retinitis proliferans. Five patients in this group had evidence of retinal edema as part of a systemic edema, associated with marked renal and cardiac disease. All of these patients showed progression of the retinitis proliferans, despite Lipoliquid therapy, and further marked visual loss.

SUMMARY

Fifty patients with diabetic retinopathy were treated with Lipoliquid, containing choline, inositol, and vitamin B_{12}. When associated with retinitis proliferans, treatment was completely unsuccessful. About half of the patients without proliferation showed no progression, and the remainder only slight progression. However, this group of patients frequently maintained their visual acuity for a long period of time, and the development of retinitis proliferans in two cases and of recurrent hemorrhages in all cases suggests that Lipoliquid is of very limited value in the treatment of hemorrhagic diabetic retinopathy.

The Lakeside Laboratories, Milwaukee, provided the Lipoliquid.

From the Department of Ophthalmology of the Mount Sinai Hospital and the Chicago Medical School.

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VISUAL CHANGES IN PROGRESSIVE EXOPHTHALMOS

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BOSTON

PROGRESSIVE exophthalmos is often called "malignant" exophthalmos, and it is sometimes referred to as exophthalmic ophthalmoplegia (Brain [12]), thyrotropic exophthalmos (Mulvany [15]), and a hyperophthalmopathic type of Graves's disease (Means [16]). In contrast to the slight exophthalmos of goiter, which may be combined with some staring, the malignant type is characterized by its progressive nature; periorbital and lid edema; diminution or lack of resiliency, elicited by palpating the eyeball; limitation of ocular motility, often causing diplopia, and retraction of the upper lid, resulting in staring. In some cases thyrotoxicosis precedes this exophthalmos, but usually by the time there are signs of progressive exophthalmos the thyroid condition is well controlled or has reached the stage of hypothyroidism; occasionally there is no thyroid history whatsoever. Fortunately, malignant exophthalmos occurs infrequently, for it is a disabling and dangerous disease and a great burden to the patient, as well as to the physician, particularly the ophthalmologist. The exposure of the cornea and the different types of ophthalmoplegia are the most frequent ocular signs with which we have to concern ourselves. There is, however, a third group of disturbances which deserve attention and which are related to the visual pathways. They are not at all unknown to the expert in the field of exophthalmos, particularly the neurosurgeon; but in the literature they are very rarely described in detail.

I wish to report on six such cases with visual changes. I have seen three of them; three have been collected by Dr. David G. Cogan,* and he asked me to include them in my report.

REPORT OF CASES

CASE 1.—A 38-year-old man.

1945: Thyrotoxicosis successfully treated.

1951: Diplopia and beginning exophthalmos of left eye. For years no thyroid symptoms (only fatigue). Thyroid tablets used all the time. Left exophthalmos becomes progressive; periorbital edema; resiliency diminished; absence of upward gaze. Vision failing (from 20/20 to 20/70). Fundus normal, including macula, but lower squares compressed on Amsler chart.

December: X-ray treatment to pituitary (six irradiations).

1952: January: Beginning and progressive exophthalmos of right eye, with progressive lid lag. Fundus and visual field normal, while in lower temporal field of left eye a disturbance starts, "as if light goes on and off."

May: Another six irradiations to the pituitary. Palpebral fissure on left becoming smaller; on right side, larger (March: O. D. 12 mm., O. S. 10.5 mm. June: O. D. 15 mm., O. S. 9.5 mm.). Vision and fundus normal in both eyes; exophthalmos almost equal on two sides (O. D. 26 mm., O. S. 25 mm. [Hertel]).

1953: Exophthalmos: O. D. 25.5 mm., O. S. 24.5 mm. Lid fissures still same. Vision and fundus normal. Most intriguing is the diplopia.

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Read before the Section on Ophthalmology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 24, 1954.

* Associate Professor of Ophthalmology, Harvard Medical School; Director, Howe Laboratory of Ophthalmology, Boston.

This 38-year-old patient suffered originally from thyrotoxicosis, was first treated with radioactive iodine and later with thyroid, and was under treatment with the latter drug when the progressive exophthalmos started, six years later, first on the left side, then on the right.

This case gives me the opportunity to comment on some visual peculiarities. There was some temporary reduction of central vision in each eye which was not complicated by a central visual field defect or an ophthalmoscopic change. This type of slight and temporary visual failure has been mentioned by different authors. We have no explanation for this change, and it has very little significance.

Another phenomenon in the visual function of this patient is worth mentioning, since the same symptom was present in the third case. In tests of the fields there was a flickering of the test object in the left eye only, and the patient had the impression of a light going off and on. In both patients this phenomenon was in the lower temporal field of the left eye, at times not quite reaching into the central region; at other examinations, reaching also somewhat into the right lower quadrant. The fundus and central vision were normal. The proptosis, which was more marked in the left eye at the time when this symptom was first observed, later manifested itself in the other eye to about the same degree, and in the third patient it was always equal in the two eyes. This type of field anomaly, the flickering, is suggestive of a disturbance in the retina. Furthermore, the metamorphopsia found with the Amsler chart in the same (left) eye of the first patient favored such an assumption. The phenomenon lasted about 15 months in this case and then disappeared.

Since it was suspected that this field defect was due to some disturbance of the retina, I wish to mention that in a few instances real retinal pathology has been seen in progressive exophthalmos. Ida Mann [1] described a patch of exudate in the macula, with vision of 6/36, in one eye. After thyroid treatment the exudate disappeared and vision improved to 6/6. Observations have been made of tension lines, ridges, or folds in the retina, similar to findings in cases of orbital tumor (Mann,[2] Walsh,[3] Steinmetz[4]); in the cases of Mann and of Steinmetz there was at the same time retinal or neuroretinal edema.

In the last century, the prominent ophthalmologist O. Becker (Sattler [5]) stated that he had found arterial retinal pulsation in many cases of Graves's disease. The only confirmation of this in recent times was given by Savin,[6] who stated that the only fundus appearance characteristic of thyrotoxicosis is arterial pulsation. In this connection, it is of interest that Braley [24] found an elevation of intraocular pressure in a number of cases.

CASE 2.—A 65-year-old woman.

1950	
January:	Beginning exophthalmos and lid swelling.
July:	Thyrotoxicosis treated with propylthiouracil. Failing vision.
1951	
January:	Thyrotoxicosis under good control. O. D.: Exophthalmos 22 mm.; acuity, counting of fingers; central scotoma; temporal pallor. O. S.: Exophthalmos 24 mm.; acuity 20/50; field normal, only weakness for colors on temporal side of fixation point; doubtful temporal pallor.
1952	Vision slowly improving; patient can read a newspaper now.
1953	
October:	Patient euthyroid. Still some exophthalmos. No diplopia. Normal resiliency of eyeballs. Patient takes thyroid tablets all the time; feels well. O. D.: Counting of fingers; central scotoma. Disc grayish white. O. S.: Vision 10/15; reads finest print. Temporal pallor.

CASE 3.—A 50-year-old woman.

1951 Hyperthyroidism with exophthalmos.

1952

April: Exophthalmos: 20 mm. O. U. Vision: O. U. 20/20. Fundi normal. Paralysis of upper gaze.

May: O. D. 20/50. Central and paracentral scotoma (Fig. 1).

August: Exophthalmos: 25 mm. O. U. Vision: O. D. 20/200; O. S. 20/20. Field defect ("off and on") (Fig. 2).

September: Vision: O. D. same; O. S. 20/50—.

1953

January: Exophthalmos: 23 mm. O. U. O. D.: 20/40; still small central scotoma; slight pallor of disc (?).
O. S.: 20/20; fundus normal; slight defect below fixation point.

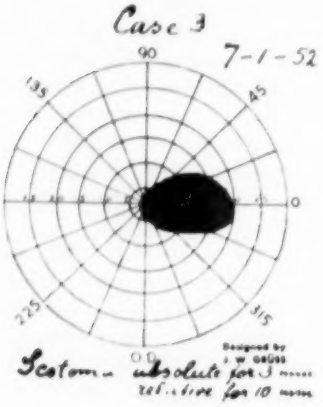

Fig. 1.—Vision 20/200.

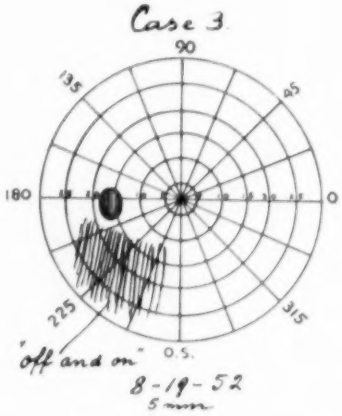

Fig. 2.—Vision 20/50.

April: O. D. 20/15; O. S. 20/20. No scotoma any longer in right eye; only relative defect in left eye.
Fundi negative. Patient takes 5½ grains (0.33 gm.) of thyroid daily.

November: Visual complaints. O. D. 20/20; O. S. 20/30.
Exophthalmos: O. D. 24 mm.; O. S. 22 mm. Relative paracentral scotoma on left eye. Pallor of disc (?).

CASE 4.—67-year-old woman.

1952

January: Hyperthyroidism, treated with radioactive iodine, then with thyroid.

1953

March: Proptosis first on right side; two weeks later on left.

June: Failing vision.

July: Exophthalmos: O. D. 21 mm.; O. S. 19 mm. Fundi normal.
O. D.: 10/200. Central and paracentral scotoma (Fig. 3).
O. S.: 20/50.

September: O. D. hand movements; O. S. 20/50.
Dx: Decompression operation (Dr. J. C. White†). After operation, O. D. 20/40; O. S. 20/30.

† Associate Professor of Surgery, Massachusetts General Hospital.

CASE 5.—A 44-year-old woman.

1951

June: Thyrotoxicosis. Exophthalmos: O. U. 26 mm. Periorbital edema. Recently failing vision. O. D. 20/30; O. S. 15/200 (? central scotoma). Fundi normal; only venous congestion.

July: Decompression operation on left side (Dr. J. C. White).

October: Exophthalmos: O. D. 25 mm.; O. S. 17 mm. Still considerable periorbital edema. Hypertropia of about 15 degrees. O. D. 20/15; O. S. 20/20.

1953

November: Patient feels very well, is able to work every day (Dr. J. McClintock). Corrected vision 20/25 for each eye. Fundi normal. Paresis of left inferior rectus and of left superior oblique muscle without diplopia. Lid edema receded, but still marked exophthalmos (O. D. 23 mm.; O. S. 19 mm. [Hertel], Dr. J. A. Cetner).

CASE 6.—87-year-old woman.

1953

Dec. 9: Periorbital swelling, redness of the eyes, and exophthalmos for four weeks. Exophthalmos: O. U. 28 mm. (Hertel). Discs normal. Veins somewhat dilated. No arterial pulsation.

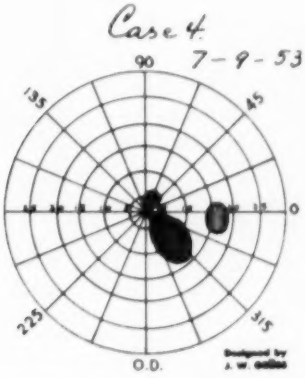

Fig. 3.—Central and paracentral scotomas. Vision equals hand movements.

Intraocular tension O. U. 20 mm. Hg. Vision on right eye counting of fingers at 3 ft. (90 cm.); on left eye 3/200. Central scotomas in both eyes, more pronounced in right one. Border of fields normal for hand movements.

Dec. 24: Edema and exophthalmos progressive.
Treatment: As yet, thyroid, 2 grains (0.12 gm.) daily. From now on, corticotropin, 20 mg. every six hours.

A few days later: Periorbital edema greatly reduced and ocular movements much better.

1954

Jan. 6: Vision on right eye 3/50, on left eye 3/20; she can read 18-point type (Lebensohn chart). Still central scotoma. Exophthalmos: O. D. 26 mm.; O. S. 28 mm.

Jan. 16: Sudden operation for abdominal complications (appendectomy, transverse colostomy). Corticotropin and thyroid discontinued.

Feb. 15: Exophthalmos about the same. No periorbital edema. Besides the heart trouble, malignant tumor of the breast, and the abdominal complications, nothing abnormal was found, and the exophthalmos was unexplained.

COMMENT

The second, third, fourth, and fifth cases all had had or still had signs of thyrotoxicosis. The sixth case, however, an 87-year-old woman with heart trouble, did not show any symptoms or signs of a present or past thyroid condition.

These five cases have one point in common, and this brings us to the main topic of this report. They all had at times such a marked reduction of visual acuity in one eye that blindness seemed to be an imminent danger. Usually the other eye also had some reduction of vision, but to a much less degree. This loss of visual acuity was due to a central and paracentral scotoma. The ophthalmoscopic picture of the disc was normal in Cases 4, 5, and 6; there was a doubtful pallor in Case 3, and in Case 2 the pallor was definite in the right eye and questionable in the left.

The second point which these cases have in common is the absence of any trace of pathology in the retina, with the possible exception of the left eye of Case 3.

There is no doubt that the visual failure was due to an involvement of the optic nerve. Absence of edema of the disc and of vascular engorgement around the disc, as well as lack of any intracranial signs, makes it most likely that the source of the optic involvement was within the orbit behind the globe. The contents of the orbit in malignant exophthalmos are under high pressure, as is manifested by the diminished resiliency. One can then speculate that great pressure must be exerted on the optic nerve near the optic foramen or in front of it.

The literature is surprisingly meager concerning this occurrence. There are a few cases of optic atrophy in the older literature (Emmert,[7] Friedmann [8]), without any description of the course of the optic disease. Foster Moore [9] probably had the same condition in mind when he mentioned retrobulbar neuritis as a complication of severe exophthalmos, as did Sattler, in 1921,[10] and Paufique, Papillon, and Guinet,[11] in their first case. Brain [12] mentioned primary optic atrophy as one of the rare complications of exophthalmic ophthalmoplegia, which he refers to as malignant exophthalmos. Lyle [13] describes two cases which are similar to ours in that there was defective vision and pallor of the disc, and in one of them there was a small paracentral scotoma. He reports his two observations together under the title "ischemia of the optic disc."

There are other observations which make it evident that the optic nerve occasionally is injured a good distance behind the globe. Naffziger [14] has found three instances of altitudinal hemianopsia; in each instance the lower half of the field was lost. It is most likely that the region of damage was near the optic foramen. In one of those patients of Naffziger,[15] the inferior half of whose visual field was lost, the central vision was reduced to counting fingers at 2 ft. (60 cm.), but the fundus did not show any pathology. Naffziger and Means [16] have also seen a case with a bitemporal defect; whether or not the chiasm was involved is undetermined, since intracranial pathologic signs are generally not known in cases of malignant exophthalmos.

While the cases which I described did not show ophthalmoscopic evidence of early optic nerve damage, there are apparently many others in which papilledema is the main feature. It may be combined with retinal hemorrhages (Naffziger,[17] Mulvany,[18] Walsh,[3] Meadows,[19] Lyle [13]) or with very marked venous engorgement (Ruedemann,[20] Ida Mann [1]). The neurosurgeon uses the presence of papilledema as one of the main indications for surgical intervention. The prominence of the disc may reach 5 D. (Poppen [21]). This papilledema seems almost invariably to be com-

bined with great loss of vision, since it is often noted that the vision improved after the treatment. More detailed data about visual acuity are given by Thomas and Woods,[22] Falconer and Alexander,[23] Lyle,[13] and Braley,[24] but rarely about a visual field.

The fact that papilledema in malignant exophthalmos is accompanied by visual failure demonstrates that in pathogenesis it differs from papilledema caused by intracranial pressure, which in the early stages has no visual complication. It must have a local source. It is also true that both types of papilledema, if the pressure is not relieved, can be followed by optic atrophy.

This local source is apparently the high tension from which the orbital contents suffer in severe exophthalmos; it is comparable to the effect of a tumor. Mulvany [18] attributes congestion and swelling of the disc to direct pressure of the swollen muscles on the optic veins. The effect on the more posterior or on the more anterior

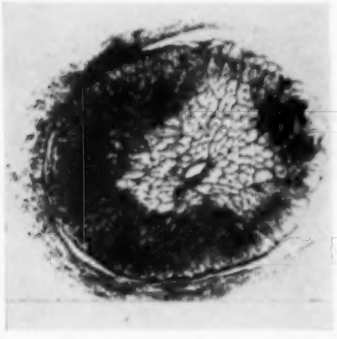

Fig. 4.—Axial degeneration of the optic nerve caused by a tumor in the meningeal sheath within the orbit. Reproduced from Schlodtmann, in Festschrift für A. V. Hippel, Halle, 1900; published by C. Marhold, Halle.

Fig. 5.—Sarcoma of the orbit not invading the optic nerve (Igersheimer, J.: von Graefes Arch. Ophth. **95**:1, 1918; published by Springer-Verlag, Berlin).

part of the optic nerve may be seen in one and the same nerve, as in an interesting observation of Hedges and Rose.[25] A 44-year-old woman had a remission of thyrotoxicosis, accompanied by central and paracentral scotomata in both eyes and reduction of vision to 20/40. Later, papilledema developed in the right eye.

Why in many cases, in spite of a high degree of exophthalmos, the vision remains intact, and why in other cases, with about the same degree of exophthalmos in the two eyes, one eye shows a much higher degree of visual loss than the other, is hard to explain. At decompression operations Falconer and Alexander found the orbital contents to be under increased pressures in some instances, in others not.

Since, as far as I know, anatomical studies of the visual pathways have never been made in this field, I shall refer for comparison to some findings in which a real orbital tumor had damaged the optic nerve by pressure alone. In the case of Schlodtmann [26] a tumor in the meningeal sheath of the second nerve was located in the posterior part of the orbit (Fig. 4). While the periphery of the cross section of the nerve looks normal, one can see an atrophy in the central part of the nerve reaching forward to the region of the central vessels. This explains a central

scotoma and a normal disc (at least for quite a while). Another patient died of a sarcoma which originated in the nasal sinuses and invaded both orbits, but did not involve the optic nerve (Fig. 5). Two months before the patient's death one could still demonstrate a great central visual defect (Fig. 6). Anatomically the nerve fibers showed simple degeneration; only in the region of the central vessels was there an enormous stasis, with dilatation of vessels and hemorrhages (Fig. 7) (Igersheimer [37]).

It seems, therefore, that in case an increased pressure in the orbit has a damaging effect upon the optic nerve in the region of, or in front of, the optic foramen, the papillomacular bundle and its surroundings are mainly disturbed. The result is failing vision with central or paracentral scotoma; the fundus is normal and only later shows pallor of the disc. In other cases, besides the damaging effect on the nerve fibers, the pressure causes stasis in the region of entrance of the

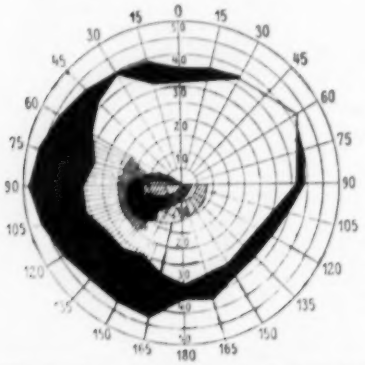

Fig. 6.—Sarcoma of the orbit. Central visual defect two months before death (Igersheimer, J.: von Graefes Arch. Ophth. **95**:1, 1918; published by Springer-Verlag, Berlin).

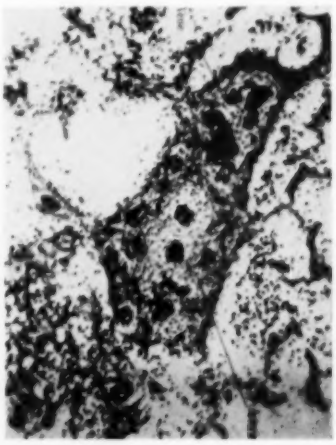

Fig. 7.—Sarcoma of the orbit. Simple degeneration of the optic nerve only in region of central vessels. Great stasis (Igersheimer, J.: von Graefes Arch. Ophth. **95**:1, 1918; published by Springer-Verlag, Berlin).

central retinal vessels in the optic nerve. The result is failing vision, probably with central or paracentral scotoma, and papilledema.

From some publications on chronic orbital myositis and orbital pseudotumor, it seems that visual changes similar to those in malignant exophthalmos may occur in these conditions (cf. cases of Benedict and Knight [37] and Ellett [38]).

I myself saw a middle-aged (49-year-old) patient who had unilateral exophthalmos, with excessive lacrimation and conjunctival injection. Exploration of the orbit was done by Dr. Bertram Selverstone, and a lymphocytic infiltration was found microscopically. The diagnosis of a lymphomatous disease was supported by the finding of a pathologic lymph node in the left axilla. Sometime later the proptosis of the right eye increased again and was combined with reduction of vision. The patient had vision of 10/20 in the proptosed eye and a relative central scotoma for red and blue. In the left eye he had 10/10 vision and a normal field. The fundus was normal in both eyes. On the Hertel exophthalmometer readings

were 26 mm. for the right eye and 19 mm. for the left eye. After 10 x-ray irradiations to the orbit, the exophthalmos disappeared totally. Vision on the right eye increased to almost 10/10, and there was no longer any scotoma.

Having discussed the pathogenesis of the visual changes in malignant exophthalmos, we now come to the highly practical question of what one must do in a case in which one eye is already greatly reduced in vision and the second eye is failing.

TREATMENT

There are several possible forms of therapy.

The first one is to wait a certain time and to continue the medical treatment, e. g., with thyroid tablets, as was done in Cases 2 and 3. Some of the cases apparently run a self-limiting course. Ida Mann had good results with conservative treatment in many of her cases.

A second form of treatment is the systemic use of corticotropin or cortisone. In Case 6, in which there was no history of thyroid involvement and the patient was too old for any heroic procedure, corticotropin was started, and after a few days the periorbital edema subsided to a high degree. The improvement of vision followed this diminution of edema. The exophthalmos, however, responded very little.

If the progressive exophthalmos cannot be controlled by medical treatment or blindness seems imminent, there are two methods which have to be considered: x-ray treatment to the pituitary and orbital decompression.

When one consults the literature on the usefulness of these two procedures, one finds that in most papers only the effect upon the exophthalmos is reported, while in only a few cases is visual pathology mentioned. Most authors feel that x-ray treatment has little value. Naffziger [28]; McCullagh, Ruedemann, and Gardner [29]; Meadows [19]; Sloan,[30] and Hedges and Rose [25] consider this treatment as not impressive or as doubtful in its efficacy. Brain [12] feels that it is satisfactory in some cases; Juler (Law [31]) saw a good result in one patient within two months. Beierwaltes [32] followed 10 cases from 6 to 48 months and noted a significant recession of the exophthalmos in 7 cases. Two temporal fields were used, and, in addition, an anterior nasal field in two patients. The total amount of radiation was 700 r per field, with a field size of 8 by 7 cm. The average interval between radiation therapy and the beginning of the recession of exophthalmos (2 mm. or more) was three months. Occasionally the treatment was repeated after several months. In one case there was visual failure, but its character is not clearly described ("black-out of right visual field"), nor is the effect of the x-rays on the vision mentioned. Hermann's [33] results have also been gratifying in a number of patients, but she stresses the necessity of using at least 3,000 r for the irradiation of the pituitary. Paufique, Papillon, and Guinet [11] suggest even 4,000 r. The difficulty in interpreting the results of x-ray treatment is demonstrated by the first case of our series. One month after irradiation, exophthalmos, puffiness, retraction of the upper lid, and ophthalmoplegia developed in the second (right) eye, and three months after the irradiation the lid retraction of the first (left) eye began to lessen, until there was a great difference between the two eyes. It is a matter of speculation as to whether these two somewhat contradictory events were in any way related to the x-ray treatment.

A much more aggressive method is the orbital decompression proposed by Naffziger,[34] or a modification of this operation. This procedure is justified only

when blindness is imminent. Under such circumstances its indication is stressed by Naffziger, Mulvany, Brain, Meadows, and others. When we as ophthalmologists are confronted with the problem, it is important that we be acquainted with the risk and the results of the operation. Besides the danger of a meningeal infection, which is very slight in these days, it is a fact that the exophthalmos after the operation often does not recede for some time and that the orbital edema increases. Therefore, it is well to protect the cornea by a tarsorrhaphy immediately after the decompression. Occasionally the exophthalmos first decreases and then returns, as in an observation of Hedges and Rose. On the other hand, we occasionally find that a bilateral exophthalmos recedes after a unilateral decompression. The experience of Naffziger, Poppen,[35] and others reveals that, in spite of persistent or increasing orbital edema, restoration of vision follows the decompression. In contrast to this optimistic view, Law noted several cases of papilledema in which the vision was diminished after orbital decompression, and Lyle supported him, although there was a marked improvement in vision after decompression in one of his cases of papilledema.

It is now of interest to look at our series and to see what one can learn from it. In the fourth and fifth cases a decompression operation was performed in the Massachusetts General Hospital. The failing vision had begun only a short time before the operation but was progressing rapidly. The immediate visual result was an excellent one in both cases. In Case 5 the success was lasting, while in Case 4 it was not possible to get later information. In Cases 2 and 3 the visual situation was also very grave, and the possibility of an operation had to be presented to the two women. It was a great responsibility for the consulted ophthalmologists, but the decision was made easy by the patients themselves, since both refused surgical treatment. What happened? The 50-year-old woman, who had greatly reduced vision (20/200) and central scotoma for over five months, regained her full vision within two or three months by continuing her thyroid therapy. The vision in the right eye of the 65-year-old patient began to fail in July, 1950; in January, 1951, she could only count fingers, and there was a central scotoma and temporal pallor of the disc. This eye did not recover; in October, 1953, the vision, visual fields, and fundus had not changed, showing that the degeneration in the optic nerve had already begun and that a decompression would probably not have saved the function at the time when we thought of an operation.

From these four observations it can cautiously be concluded (1) that even a great loss of central vision can be restored with and without orbital decompression so long as ophthalmoscopy does not show signs of optic degeneration, and (2) that the prognosis is guarded if the disc shows some pallor. In Case 2 the disc of the second eye had a doubtful pallor, but there was no scotoma and the reduction of vision was moderate; this eye recovered totally under medical treatment (propylthiouracil).

In very desperate cases (Shannon and Hunt[36]; Hermann[33]) both procedures have been used on the same patient—irradiation to the pituitary first, followed by decompression, or vice versa.

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IDIOPATHIC LIPEMIA RETINALIS

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LIPEMIA retinalis is that condition found ophthalmoscopically in a patient with hyperlipemia in whom the blood lipids have become sufficiently increased to alter the appearance of the retinal blood column, the arteries and veins appearing as broad cream-colored ribbons against a milky background. Hyperlipemia occurs as the result of an abnormal increase in the neutral fats, the serum developing a milky appearance when the neutral fat content reaches about 500 mg. per 100 cc. Lipemia retinalis, however, does not appear until the neutral fat content is much higher.

According to Thannhauser,[1] the amount of lipid substance in the serum is dependent upon the following factors: (1) the absorption of fat from the intestine; (2) the migration of fat from fat depots to the organs of fat disintegration; (3) the deposition of fat in subcutaneous and other fat-storing tissue; (4) the speed of fat disintegration in the organs, that is, the balance between fat transportation and fat combustion, and (5) the disturbance of the lipid metabolism within the cell. Hyperlipemia may result as a clinical symptom from a disturbance of any one of these five processes.

Thannhauser [2] describes three basic types of hyperlipemia: (1) physiologic hyperlipemia, following intake of an excessively high fat meal; (2) transportation hyperlipemia, as seen in diabetes mellitus, chronic alcoholism, starvation, severe anemias and leukemias, lipid nephrosis, and poisoning, as with phosphorus, chloroform, and carbon tetrachloride, and (3) retention hyperlipemia, this being characterized as an essential, or idiopathic, hyperlipemia. The cause of the idiopathic hyperlipemia is unknown.

Heyl,[3] in 1880, first described the clinical picture of lipemia retinalis. Since that time, of approximately 78 reported cases of lipemia retinalis, 65 have occurred in patients with diabetes mellitus and 13 have shown no clinical or laboratory findings suggestive of diabetes mellitus (Wagener [4]; Dunphy [5]; Bernstein and associates [6]; Goodman, Shuman, and Goodman [7]; Kauffman [8]; Lepard [9]; Grossmann and Hitz,[10] and Everett,[11] 1 case each; Holt, Aylward, and Timbres,[12] 2 cases; Groom and Rucker,[13] 3 cases).

Wagener [4] described a case of hyperlipemia with lipemia retinalis in a 9-year-old boy who had received radium therapy for lymphatic leukemia. Holt and associates [12] reported two cases of idiopathic lipemia retinalis occurring in an 11-year-old girl and her 2½-year-old brother. In the girl, the lipemia was associated with hepatomegaly, splenomegaly, psoriasis, peculiar ulcerations of the skin, and malnutrition. Lipemia retinalis occurred when the fats rose to 2.5 to 3%. Examination of the boy showed lipemia retinalis associated with an enlarged liver and spleen and a blood fat of 3%. The author suggested that the lipemia in these cases is due to a defective mechanism for removal of blood fat by the liver, a mechanism in which a humoral factor appears to be concerned.

Goodman [7] reported a case of idiopathic lipemia with secondary xanthomatosis, hepatosplenomegaly, and lipemia retinalis in which all laboratory tests were normal and no cause for the lipemia could be found. Kauffman [8] reported a case of lipemia retinalis in a nondiabetic 25-year-old Negro man having alcohol gastritis and vascular hypertension. In Lepard's [9] case of lipemia retinalis without evidence of diabetes mellitus, the patient was 6 years old and examination revealed an enlarged spleen and liver.

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Grossmann [10] reported a case of severe lipemia retinalis in a 55-year-old man having idiopathic hyperlipemia. When first discovered, the blood fat was 13.13%. The lipemia retinalis was seen receding when the lipid content fell to 4.06% and disappeared when it fell to 2.12%.

'Groom and Rucker reported three cases of nondiabetic lipemia retinalis—one in a 59-year-old white man presenting the picture of idiopathic hyperlipemia, another in a 33-year-old white man who was a chronic alcoholic, and a third in a 7-month-old white boy who was afflicted with Niemann-Pick disease. The author stated that in lipemia retinalis the appearance of the retinal vessels depends upon the presence of an excessive concentration of neutral fat in the blood, that other lipids (cholesterol, cholesterol esters, and phospholipid) may be present in abnormally high concentration, but that they are incidental and do not contribute to the ophthalmoscopic picture.

Dunphy [5] reported the case of a 47-year-old man with idiopathic hyperlipemia showing lipemia retinalis and secondary xanthomatosis. He stated that the lipemia retinalis paralleled the neutral fat level of the serum. Although it was impossible to get blood samples at the exact time the lipemia retinalis appeared and disappeared, the retinal vessels always appeared normal when the neutral fat dropped below 2,000 mg. per 100 cc. and were found to be milky or creamy when it rose to 2,500 mg. per 100 cc. or above.

Everett [11] reported the case of a 3½-year-old boy having nondiabetic lipemia retinalis. He stated that the milky quality of lipemic serum is due to the presence of lipid droplets of a size greater than one-fourth the wave length of visible light, that in a lipemic serum the colloidally suspended lipids coalesce to form visible droplets and a milky serum results.

Various investigators have attempted to correlate the concentration of the blood lipids with the appearance and disappearance of the retinal lipemia. Wagener [4] stated that lipemia retinalis appeared when the fat content reached 4 to 5%; Holt, Aylward, and Timbres,[12] between 2.5 and 3%; Igerscheimer,[14] 3%, and McCann,[15] 9.5%, with the condition disappearing in his case at 10.8%. McKee and Rabinowitch [16] noted that the fundus did not return to normal until the blood fat had fallen to 1.3%; Chase,[17] when it was between 1.42 and 1.13%. Parker and Culler [18] reported lipemia retinalis appearing when the fat content was 3.5% and disappearing when it reached 2.5%, while Lepard [9] noted its appearance at 4.25% and its disappearance below 2.8%. Although there is variation as reported by different authors, lipemia retinalis appears approximately when blood fats increase to 3.5% and disappears when these fats decrease to below 2.5%.

Parker and Culler,[18] in a series of 38 cases of lipemia retinalis, found acidosis present in all but 2 patients. Marble and Smith [19] stated that lipemia retinalis occurs usually in patients who are acidotic or who have recently been acidotic, but that it does not parallel the degree of acidosis and may persist after acidosis has disappeared. According to Falls,[20] acidosis is necessary to the phenomenon of emulsification. Igerscheimer [14] said that the suggestion that there is no retinal lipemia without acidosis of the blood is not tenable. Grossmann [10] stated that, although acidosis may usually be associated with hyperlipemia, as noted in diabetic persons, it is not an important factor in the production of lipemia retinalis, which occurs in the condition known as idiopathic, or essential, hyperlipemia.

The associated presence of xanthoma eruptivum has been noted in reported cases of lipemia retinalis. The lesions are pinhead- to pea-sized, with yellow apexes; they have red bases and surrounding inflammatory areolas and may become confluent. Dunphy [5] noted that in his case, which showed secondary xanthomatosis, the cutaneous lesions occurred only when the cholesterol level was markedly elevated and disappeared when the cholesterol level approached normal, even though the neutral fat level remained high. He stated that this particular type of xanthomatosis ap-

pears to be dependent upon a hypercholesteremia in conjunction with a high neutral fat level.

Clinically, the first change in the retinal vessels is seen in the far periphery, where the arteries and veins take on a milky appearance, which gradually extends centrally to the disc. When the picture is disappearing from the fundus, the changes occur in reverse order. As the condition progresses, the vessels appear larger, are ribbon-shaped, and there is considerable difficulty in differentiating arteries from veins. If the choroidal vessels are involved, the fundus takes on an ivory hue.

The presence of lipemia retinalis does not carry with it a poor prognosis, but in those patients with diabetes mellitus it does indicate poorly controlled diabetes. There is no disturbance of retinal function and no microscopic proof that hyperlipemia damages the retina.

REPORT OF A CASE

S. V., a man aged 30, Jewish, complained of an eruption over the buttocks and thighs and hyperlipemia, first noted seven months previously, when the serum of a sample of blood drawn for a routine Kahn test for syphilis was milky-white. There were no visual complaints. The past history and family history were essentially negative.

Ocular Examination.—Visual acuity, 20/20. The external eye was normal. Fundus examination revealed widened, milky-white arteries and veins, difficult to differentiate, the entire retinal vascular system being involved. The picture was typical of lipemia retinalis.

Physical Examination.—The patient was a well-developed, healthy man who showed no physical abnormalities other than multiple yellow-tipped papules, varying from pinhead to pea size, with reddish bases, distributed over the buttocks, thighs, and legs, typical of xanthoma eruptivum. The spleen was slightly enlarged.

Laboratory Data.—The findings in the dextrose tolerance test, in milligrams per 100 cc., were reported as follows: fasting, 74.6; one-half hour, 99.6; one hour, 83.3; two hours, 72.2, and three hours, 67.6. Urinalysis was negative for sugar, albumin, acetone, and diacetic acid. Blood drawn had a milky-white appearance. The red, white, and differential blood cell counts were within normal limits. The blood Kahn test for syphilis was negative. The blood cholesterol was 641 mg. and the total plasma lipids 5.6 gm., per 100 cc. The roentgenogram of the chest was reported as normal. Roentgenograms of the long bones of the legs and forearms failed to show any abnormality. The basal metabolic rate was within normal limits.

Subsequent Course.—The patient was placed on a diet of 45 gm. of protein, 18 gm. of fat, and 210 gm. of carbohydrate and the fundus observed daily. Seven days later the blood cholesterol was 510 mg. and the total plasma lipids 3.44 gm., per 100 cc. The vessels about the disc had now regained their normal appearance, but the finer peripheral branches still showed evidence of lipemia retinalis. On the 14th day the fundus was entirely normal; the blood cholesterol was 312 mg. and the total lipids 2.55 gm. per 100 cc. The diet was then changed to 45 gm. of protein, 100 gm. of fat, and 30 gm. of carbohydrate. Two months later the fundus examination was normal; the cholesterol was 270 mg., and the total plasma lipids 2.52 gm., per 100 cc. During this time the lesions of xanthoma eruptivum showed marked regression, and multiple urinalyses were reported negative for albumin, sugar, acetone, and diacetic acid. The patient has not been seen subsequently.

SUMMARY

This case is the 14th reported instance of nondiabetic lipemia retinalis, showing, in addition, slight enlargement of the spleen and xanthoma eruptivum. The lipemia retinalis completely disappeared when the total plasma lipids were reduced to 2.55 gm. per 100 cc. of plasma. The lesions of xanthoma eruptivum regressed under the dietary regime. There was no significant change in the size of the spleen.

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CORRELATION OF VISUAL ACUITY AND ABSOLUTE LUMINANCE THRESHOLD IN RETINITIS PIGMENTOSA

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IN RETINITIS pigmentosa, pigment first appears at the equator and expands as a widening ring, encroaching upon the macula and the ora serrata. Pigment is very rarely seen in the macula itself, however, and when present is probably a manifestation of concurrent degeneration of the macula or of a healed choroiditis involving the macula.[1] Despite the frequent absence of pigmentation in the macula, this structure is functionally impaired, as is shown by a reduction in visual acuity always observed in later stages of the disease.[1] That macular function is reduced in early stages as well has been demonstrated by measurements of the absolute luminance * threshold by Mandelbaum [4] and by Haig and Saltzman.[5] Using a white test light subtending 3 degrees of visual angle and located at various angles in the horizontal meridian, Mandelbaum observed that in all of 17 cases the foveal region was involved, even in one very mild case. He concluded that "sparing of the macula" is only relative. Our own study of 25 cases of various degrees of severity confirmed his findings. We used a 2-degree test light, which with central fixation practically limited the measurements to the rod-free portion of the fovea. Thus, the foveal cones are evidently impaired at all stages of the disease, and a corresponding reduction in visual acuity should occur.

The present study undertakes to demonstrate this relation by comparing corrected acuities with absolute luminance thresholds for red light at various stages of the disease.

METHODS

For threshold measurements a modified Hecht-Shlaer dark adaptometer was used.[6] The fixation light was remounted in order to facilitate rapid changes in its position. The test light subtended 2 degrees of visual angle, thus practically confining the region tested during central fixation to the rod-free area of the fovea. The white test light was filtered through a Wratten 88 red filter, which transmits only wave lengths in excess of 680 mμ, thus further limiting the response to that of the cone mechanism.† The duration of the test flash at each exposure was 0.2 second and was controlled by a Wollensack Rapax shutter.

Each threshold test was preceded by a 30-minute stay in the dark, during which the patient was familiarized with the technique of observation and preliminary records were obtained. While the patient gazed at the fixation light, the test light was exposed for 0.2 second and the patient reported whether he saw the flash. The luminance was then varied by moving the photometric wedge, and the patient again reported whether he saw the flash. This procedure was repeated until a threshold value was determined. The luminance that was seen 9 times in 10 trials was taken as threshold. The position of the fixation light was varied on both sides of the fovea in the horizontal axis out to 20 degrees, and thresholds were obtained at each position. During foveal measurements the fixation light was dimmed as much as possible and the threshold redetermined at least three times.

Visual acuity was determined by standard Snellen test type procedure after full correction of refractive errors. The luminance of the chart was 16 millilamberts (ca. 15 ft.-c.), and the distance was measured in feet. All visual acuity measurements were made by one observer (S. L. S.) at the clinic and all threshold measurements by the other (C. H.) in the laboratory. The results were not compared until all measurements were completed.

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* The unit of luminance is the lambert, or $1/\pi$ candle per square centimeter, one millilambert being numerically equivalent to 0.929 ft.-c.[2] In order to avoid negative logarithmic values, some years ago we adopted a very small unit, the micromicrolambert, or 10^{-9} millilambert.[3] This unit is used in the present study.

† References 7 and 8.

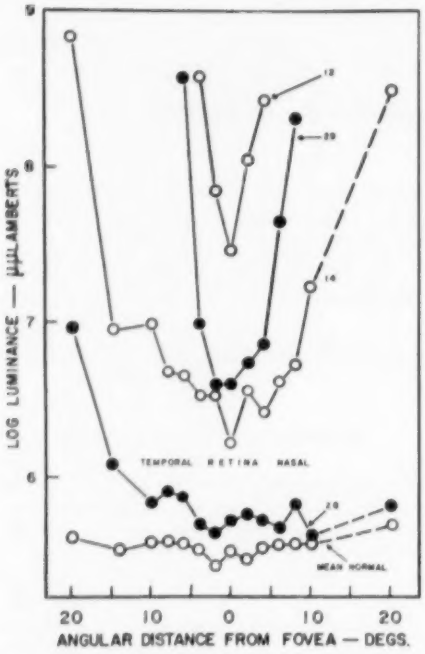


Fig. 1.—Examples of red test object retinal threshold contours for four patients having retinitis pigmentosa of varying degrees of severity. The case numbers are indicated by arrows. The lowest curve is the arithmetic mean for 10 normals. The visual acuities from the topmost curve downward are, respectively, 0.05, 0.5, 0.8, and 1.0.

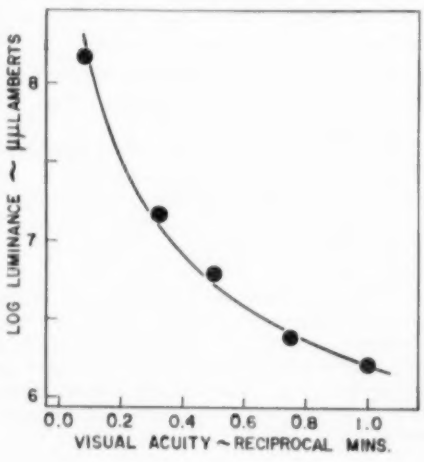
The subjects were 39 of the 47 patients of our previous report.[9] Specifically, they were patients 1 to 14, 17, 19, 21, 25 to 29, 31, 33 to 41, and 43 to 49 in that report. This paper may be consulted for particulars regarding age, duration of disease, uncorrected visual acuity, visual fields, intercurrent diseases, and other details. In the selection of patients for the present study, those having conditions likely to invalidate threshold or acuity measurements were rejected.

RESULTS

Retinal Threshold Contours.—In Figure 1 are shown typical results as exhibited by four of the patients (12, 14, 28, and 29) in different stages of the disease. All have extrafoveal thresholds well above mean normal. The foveal thresholds are also above normal. Moreover, in one example (Case 28) the foveal threshold is elevated at least as much as the thresholds of the nasal periphery. All told, 4 of the 39 patients had foveal thresholds which were elevated as much as the thresholds of certain portions of the periphery. In such cases we may say that certain extrafoveal regions are "spared" at least as much as the fovea.

The Fovea.—The accompanying Table gives the individual visual acuities and foveal thresholds for 73 eyes of the 39 patients. Acuities are expressed as the reciprocal of the visual angle in minutes, as well as in Snellen notation. For convenience in formulating the relation between the two variables, the visual acuities have been grouped in five equal class intervals of 0.200 width. A glance at the Table shows that low thresholds are correlated with high acuities. For a mean acuity decrease of 12.5 times, the threshold rises by a factor of 88. Thus, the change in threshold is seven times as great as the change in acuity. It is also seen that only the milder cases show no measurable deterioration of acuity or of foveal threshold, only 11 eyes having acuities of 20/20 or luminance thresholds below highest normal (5.92). Despite the large scatter of the threshold data, the correlation coefficient and its standard deviation for the individual values of luminance threshold as a function of acuity

Fig. 2.—Visual acuity as a function of the foveal luminance threshold for red light, from the data of the Table. The circles are the mean values obtained from 11 to 23 eyes in each of five class intervals. The curve was computed from the equation $(B - 4 \times 10^5)\ V^2 = 1.24 \times 10^6$.



Relation Between Visual Acuity and Absolute Threshold Luminance at the Fovea *

Reciprocal of visual angle (V), min.	1.000	0.800	0.667	0.500	0.400	0.333	0.286	0.250	0.200	0.100	0.070	0.050	0.050	0.030	0.015
Snellen scale, ft.	20/20	20/25	20/30	20/40	20/50	20/60	20/70	* 20/80	20/100	20/200	14/200	12/250	10/200	6/200	3/200
Threshold luminance (B), log lamberts	4.96	5.67	5.34	6.21	6.55	6.39	5.91	6.67	6.14	6.42	8.18	7.52	6.77	7.49	8.10
	5.00	5.68	5.80	6.34	7.45	6.30	6.87	6.93	8.13	6.54	....	7.63	7.17	....	8.81
	5.16	5.89	6.24	6.41	7.45	7.52	....	7.61	8.13	7.13	....	7.63	7.30	....	9.17
	5.38	6.02	6.51	6.47	....	....	....	....	....	7.17	....	8.10	7.61	....	....
	5.38	6.12	6.51	6.70	....	....	....	....	....	7.91	....	....	7.78	....	....
	5.89	6.20	6.51	6.72	....	....	....	....	....	8.04	....	....	....	....	....
	6.08	6.21	6.67	6.74	....	....	....	....	....	....	....	....	....	....	....
	6.18	6.43	....	6.80	....	....	....	....	....	....	....	....	....	....	....
	6.51	6.51	....	7.36	....	....	....	....	....	....	....	....	....	....	....
	6.51	6.69	....	....	....	....	....	....	....	....	....	....	....	....	....
	6.86	6.73	....	....	....	....	....	....	....	....	....	....	....	....	....
	....	6.73	....	....	....	....	....	....	....	....	....	....	....	....	....
Mean $B \times 10^{-6}$	1.64	2.41		6.22		14.47						144.19			
Standard error †	±0.43	±0.36		±2.19		±4.49						±66.70			
Mean V	1.00	0.75		0.50		0.32						0.08			
Standard error †	±0.00	±0.02		±0.00		±0.02						± 0.01			

* Two-degree red test object with central fixation and 0.2 second exposure; 39 patients; 78 eyes.
† Standard error of the arithmetic mean $= (\Sigma x^2/N^2)^{1/2}$, where x is the deviation from the mean and N the number of observations.

was found to be -0.67 ± 0.06. The probability of this degree of correlation occurring by chance is practically zero (x value of the normal error function = 5.96).[10]

Figure 2 is a plot of the logarithm of the arithmetic mean of the luminance against the arithmetic mean of the acuity in each class interval. It is seen that as the threshold approaches infinity, the acuity tends to zero. The curve was computed from the data and has the form $(B - B_m)\ V^2 = K$, where B = threshold luminance, V = acuity, and B_m and K are constants having the values 4×10^6 and 1.24×10^8, respectively. This equation has been derived (Haig[11]) from the probable relations of the foveal cone population density to visual acuity and to luminance threshold.

SUMMARY AND CONCLUSIONS

The foveal acuity and the absolute luminance threshold of the fovea and of the peripheral retina were determined for 73 eyes of 39 patients with retinitis pigmentosa of various degrees of severity.

The foveal threshold was elevated and the acuity reduced in fairly early stages of the disease. The fovea is therefore spared in only a relative sense.

The mean foveal threshold increase was seven times as great as the mean acuity decrease. Hence, foveal threshold measurements are a more sensitive index of the progress of the disease than are acuity measurements.

The relation between foveal threshold and acuity follows a regular course, which may be expressed in mathematical terms.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

PECULIAR INFLAMMATION OF EXTERNAL EAR ASSOCIATED WITH CONJUNCTIVITIS AND SCLEROKERATITIS

THE OCCURRENCE of disease of the ears in association with ocular disease has been well known for many years. The association of vestibuloauditory symptoms with interstitial keratitis, both syphilitic and nonsyphilitic, is well recognized. Less common, but equally well recognized, are the vestibuloauditory symptoms associated with bilateral uveitis, both in sympathetic ophthalmia and in the Vogt-Koyanagi syndrome. The association of deafness and retinitis pigmentosa is well known. Although these diseases, as well as others, are well recognized to have involvement of the eyes and the ears, the exact pathogenesis of most is in considerable doubt.

It has been thought worth while, therefore, to report two cases of peculiar inflammatory involvement of the eyes and ears. We have been unable to find any similar cases reported in the literature. The nature of the disturbance in the reported cases is not known. Perhaps the recognition and more careful study of further cases may shed some light on the peculiar association of ocular and aural disorders.

REPORT OF CASES

CASE 1.—H. C. (J. H. H. #602115), a 20-year-old Negro, was first seen in the Wilmer Institute dispensary because of pain and redness of the right eye. He stated he had been well until two weeks previously, when he noted the onset of pain and redness of the right eye. These symptoms persisted. One week previously he had noted the onset of painful swelling and redness of the right ear. Examination was entirely normal except for the right eye and the right ear. Vision was 20/20. There was slight erythema and induration in the periorbital area. The palpebral and bulbar conjunctiva was markedly injected. There were several small infiltrates at the limbus. The cornea did not stain with fluorescein. There were no K.P.'s, and the aqueous ray was negative. The remainder of the ocular examination was entirely normal. There was a slight watery conjunctival discharge. Conjunctival culture showed a moderate growth of hemolytic Staphylococcus albus. Scrapings from the limbus showed a few eosinophiles and numerous lymphocytes. There were no inclusion bodies. A small preauricular lymph node was palpated on the right. The right ear presented a remarkable appearance. It was diffusely swollen to approximately one and a half times its normal size. The ear was rather tender and was warm and erythematous.

One week later the patient was again seen in the dispensary. He was asymptomatic. The right ear was entirely normal. There was very minimal residual injection of the conjunctiva, but examination was otherwise entirely normal.

CASE 2.—C. S. (J. H. H. #452645), a 46-year-old married Greek truck driver, was admitted to the Wilmer Institute on Feb. 28, 1948, because of painful eyes and ears of six days' duration.

From the Wilmer Ophthalmological Institute, The Johns Hopkins Hospital and University.

Six days before, on awakening the patient had noticed redness, pain, and swelling of both ears and pain and redness of the left eye. One day later the right eye became red and painful. The symptoms progressed in spite of the use of hot and cold compresses at home. The patient denied having had known trauma, decreased vision, constitutional symptoms or previous similar episodes.

General medical examination was entirely negative except for slight, nontender adenopathy of the cervical, preauricular, axillary, and inguinal lymph nodes. Blood pressure was 150/95. Both ears presented an astonishing picture. They were swollen about one and a half times their normal size, and were red, edematous, and tender to touch. Hearing was normal. Examination of the eyes showed marked redness and edematous swelling of the bulbar and palpebral conjunctiva on both sides. There was a watery conjunctival discharge and marked circumcorneal congestion. There were localized areas of episcleritis in both eyes. There were minimal superficial infiltrates of both corneae near the limbus. There were small cellular K.P.'s on both corneas; the slit lamp rays were 1+, and there were cells in the anterior chamber. The

irides and lenses were normal. The media were clear, and examination of the fundi was negative. Visual acuity and visual fields were normal. Intraocular tension was normal.

Laboratory studies were nonrevealing. The white blood cell count was 5,250, with a normal differential count. NPN and fasting blood sugar were normal. Albumin was 4.6 gm. and globulin 2.3 gm. per 100 cc. Urine examination was negative. S.T.S. was negative. The chest x-ray was negative. The patient was insensitive to 10 mg. of OT. Brucella skin tests were negative. The Frei test and histoplasmin skin tests were negative. Uric acid was 3.5 mg. per 100 cc. Cultures from the conjunctiva showed a growth of diphtheroids.

There was steady and gradual decrease of the ear symptoms, with desquamation of the skin over the ears. The scleroconjunctivitis gradually improved. The cells in the anterior chamber rapidly disappeared, and on discharge, 12 days after admission, the patient was entirely asymptomatic.

One month after admission the patient was still asymptomatic. There was minimal injection of the conjunctiva over the site of the previous scleritis. Otherwise, examination was entirely negative.

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HEMANGIOMA OF THE OPTIC DISC

ANGIOMATOUS tumors of the optic disc are relatively rare. Of the eight cases in the literature for which there are pathological reports, the diagnosis of von Hippel's disease was made in six * and of endothelioma in the other two.† There were seven additional cases for which there are only clinical reports without follow-up study. It is interesting to point out the striking resemblance between the picture in the case herein reported and those in the cases of Niccol and Moore,[2] Reese,[6] and Neame.[11]

REPORT OF CASE

The patient, a 26-year-old white woman, was first seen by us in the ophthalmology clinic of the United States Naval Hospital, Philadelphia, on Aug. 22, 1952, when she presented herself for a routine refraction. She had no complaint, and her current prescription was three years old.

Angiomas of Optic Disc

Year	Author	Age	Sex	Pathological Report	Clinical or Pathological Diagnosis	Symptoms If Eye Retained
1912	Schieck [7]	26	M	Yes	Endothelioma	
1920	Sidler-Huguenin [8]	3	M	Yes	Endothelioma	
1933	Carr and Stallard [1]	13	M	Yes	Von Hippel's disease	
1934	Niccol and Moore [2]	32	M	Yes	Von Hippel's disease	
1943	Cross [3]	29	F	Yes	Von Hippel's disease	
1946	Wilder [4]	28	M	Yes	Von Hippel's disease	
1949	Souders [5]	40	M	Yes	Von Hippel's disease	
1951	Reese [6]	55	M	Yes	Von Hippel's disease	
1901	Hartridge [9]	25	F	No	Venous angioma of disc	Defective visual acuity for many years
1938	Feig [10]	45	F	No	Angioma retinae	Loss of visual acuity for two years
1948	Neame [11]	7	F	No	Von Hippel's disease	None
1945	Whiting	..	..	No	Von Hippel's disease	None
1945	Whiting	..	..	No	Von Hippel's disease	None
1948	Frandsen [12]	33	F	No	Haemangioma retinae	Poor visual acuity
1951	Reese [6]	5	M	No	Cavernous hemangioma of disc	Repeated small hemorrhages

The visual acuity was recorded as 20/40 (6/12) O.D. and 20/30— (6/12.5) O.S., correctable to 20/20 (6/6) in each eye with the following combination of lenses: O.D.: —0.75 sph. ⊂ —0.25 cyl. axis 180; O.S.: —0.75 sph. External examination of the eyes was completely within normal limits. Ophthalmoscopic examination showed nothing remarkable except for a reddish-purple mass covering the nasal half of the left disc. This tumor was elevated approximately 4 D., was highly vascular, and was composed of numerous small round masses, giving the entire lesion an appearance not unlike that of a cluster of grapes or a raspberry (Figure). The vitreous was clear, and there was no evidence of any disturbance in the retinal circulation. Visual field studies revealed nothing more than a slightly enlarged blind spot in the left eye with 20/1000 and 1/1000 white test objects. The intraocular tension was not elevated.

* References 1 through 6.

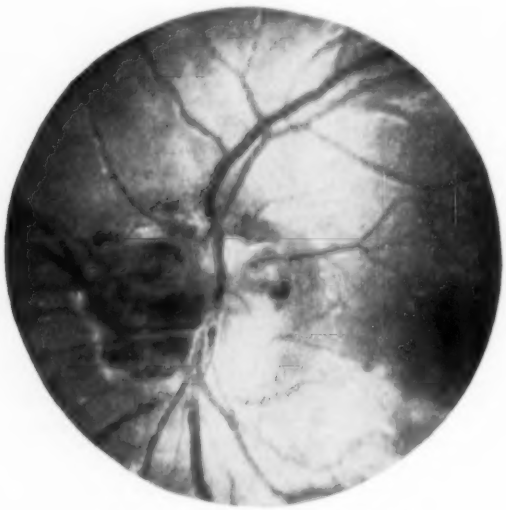
† References 7 and 8.

The patient volunteered the information that the lesion had first been noted in February, 1951, during a period of hospitalization for acute appendicitis. Her family history was negative for any disease of a hereditary nature.

On Jan. 26, 1954, the patient returned to the clinic on a routine visit. She was asymptomatic, and the visual acuity, visual fields, and ophthalmoscopic picture had remained unchanged. Attempts to produce a change in the size or prominence of the angioma by digital pressure on the globe, Valsalva maneuver on the part of the patient, and postural changes were unsuccessful.

A skin survey showed numerous elevated, reddish-purple lesions on the trunk, which measured 1 to 3 mm. in diameter, and which under a magnification of 18 diameters had a raspberry-like appearance, similar to that of the lesion in the left eye. X-rays of the skull were completely normal.

An ophthalmoscopic examination was made three months later, one day following the delivery of the patient's first child. There was no change in the appearance of the lesion in the left eye. The patient has not been seen since her discharge from the hospital following delivery.



Hemangioma of the left optic disc.

COMMENT

We have observed this patient, with an angioma of the left optic disc, for over a year and a half and have noticed no change in the size or shape of the lesion. The lesion was first recognized 18 months prior to its being seen in our clinic. The patient has been asymptomatic before and since our observations. Associated skin lesions when viewed under a magnification of 18 diameters showed similar structure. Changes in arterial and venous pressure in the eye induced by the methods stated failed to change the size and shape of the lesion.

The diagnosis of Dr. Francis H. Adler was cavernous hemangioma of the disc.

LIEUTENANT ERNEST F. WALLNER JR. (MC), U. S. N.
LIEUTENANT LEMUEL T. MOORMAN (MC), U. S. N.

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CONGENITAL EVERSION OF THE UPPER EYELIDS

CONGENITAL eversion of the upper eyelid is of considerable rarity in the ophthalmic literature. It has recently been reported by Ostricker and Lasky [1] in the first case of its kind to be recorded. The authors also state that there are a few scattered cases of congenital ectropion of the eyelids in the literature of the past 20 years, but these have all been associated with other anomalies and are quite unlike the complete eversion of the eyelids.

REPORT OF CASE

A full-term Negro boy was delivered of a 14-year-old, primigravida clinic patient (Rh positive; S.T.S. negative) on March 3, 1953. Delivery was relatively uneventful except for slight arrest of the head on the perineum. Ocular examination revealed markedly chemotic, thickened, edematous, totally everted upper eyelids (Figure). No other anomalies were noted.

Continuous saline soaks, chlortetracycline (Aureomycin) ointment, and the use of adhesive strips failed to restore the lids by the fourth postnatal day. On the fifth day the child was

Totally everted upper lids at 5 days of age.

taken to the operating room, and, with very light ether anesthesia, the upper and lower eyelids of both eyes were sewn together. Three mattress sutures of black silk with small rubber dams were placed on the outer, middle, and inner aspects of the lid margins.

On the seventh postoperative day, the sutures were removed, revealing complete subsidence of all previous ocular pathology and two normal upper eyelids. The eyes closed tightly, with the lids in good apposition, even when the child was crying. The baby was discharged on the 17th postnatal day, after an uneventful recovery. In subsequent monthly follow-ups, the child revealed no further ocular abnormalities or significant findings.

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Annual Reviews

LIDS, LACRIMAL APPARATUS, AND CONJUNCTIVA

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LACRIMAL APPARATUS

Congenital Anomalies

THE EMBRYOLOGY and developmental anatomy of the nasolacrimal system seems to be well established. However, Waldapfel [1] states that there is a solid rod of buried cells which is present between the nasolacrimal sac and the nose. It is interesting to note that this tube or rod of cells may not open until sometime after birth. Waldapfel believes that this solid epithelial rod may extend throughout the entire system from the canaliculus, the sac, and the nasolacrimal duct and that it canalizes sometime during the early neonatal period. He bases this assumption on the injection of iodized oil U. S. P. (Lipiodol), after which x-ray pictures were taken. This procedure was followed by the usual probing and irrigation of the lacrimal sac. He presents nine cases of congenital dacryostenosis in children varying in ages from 3 to 9 months of age. All the cases presented the well-known symptoms. He feels that atresia is commoner in the upper end of the nasolacrimal duct, but obstruction may also occur at the lower end of the duct, particularly with debris. Waldapfel's results might have been different had he used a lighter radiopaque fluid than iodized oil.

Waldapfel's [1] findings were more or less confirmed by Nordlöw and Vennerholm,[2] who observed 100 cases of obstruction of the lacrimal passages in a 10-year period from 1943 to 1953. Eighty-four per cent of these patients developed epiphora during the first month of life and the remainder during the first 13 months of life. While atresia of the nasolacrimal duct was commonest in their series, four patients were seen with atresia of the inferior punctum. They were able to open the puncta by dilation in only one of these patients. Several patients were seen with atresia of the canaliculis, which could be opened successfully. It is interesting to note that we recently saw a patient in our clinic who had marked epiphora. There was no evidence of either an upper or a lower punctum. I opened the lacrimal sac and was able to pass a probe in both directions, down into the nose and back through the canaliculus to the lower lid. At the lower lid, the area where the punctum should have been was covered with a thin layer of skin. It appeared to me that the entire lacrimal system was open except for the puncta.

There continues to be considerable controversy regarding the management of congenital occlusion of the tear duct. Most ophthalmologists are agreed that the nasolacrimal duct should be probed early, preferably before the end of the second month of life. Nelson [3] wishes to stress early probing, but, in addition, he emphasizes that no trace of blood should be allowed to remain either in the lumen of the duct or in the nostril, since hemorrhage, when it is present, becomes organized and is reinfected, resulting in a more frequent recurrence of occlusion of the nasolacrimal duct. All traces of blood should be washed out. As was noted in last year's review,[4] I still prefer to wait until the baby is 3 or 4 months of age, or until infection intervenes, before probing is done.

Milder and Demorest [5] present an interesting study of the nasolacrimal system by using ethyl iodophenylundecylate injected through the lower canaliculus. Pantopaque was chosen after testing other contrast media. The patient is placed in an upright sitting position in front of the cassette; the conjunctiva is anesthesized, and Pantopaque is injected into the lower canaliculus. The first film is taken 5 to 10 seconds after withdrawing the lacrimal needle, and the second film

after 20 to 30 seconds. The authors believe that the follow-up film is most important, since it gives considerable information regarding abnormal function of the nasolacrimal apparatus. They found a wide variation in the normal, but the basic normal was certainly very much as it has been described before in the literature. When more than a trace of residual Pantopaque is present in the follow-up film, some abnormal function is indicated. The authors think the ophthalmologist should personally inspect the film. Truchot and co-workers [6] devised an ingenious method to obtain x-rays of the nasolacrimal duct. Ordinary dental film is used, with the sensitized surface placed in the anterior plane. The dental film is held with the back teeth toward the roof of the mouth, but closer to the soft palate. By using this technique, it is possible to visualize by axial projection the osseous canal. The x-ray beam is aimed so that it will be axial with the lacrimal duct, following a line through the second molar. With a little practice the pictures obtained are very good, and the osseous canal can readily be seen. Iodized oil and other radiopaque solutions can be used with this technique to visualize the duct and the sac. The authors feel that this method is a valuable means of obtaining information of help in determining treatment.

Polyethylene tubing and other plastic materials are still very popular among ophthalmic surgeons, not only for repair of the lacrimal canaliculi but also for keeping the nasolacrimal drainage canal open. The various procedures were summarized in last year's review,[4] and very little additional information was available this year. Clark,[7] however, reports some of his experience with use of plastic tubes. He uses a trochar to pass the tube through the nasolacrimal duct, by way of the superior canaliculus, for the inferior canaliculus is easily torn and may be split, whereas the upper canaliculus is not readily split when the large trochar is used. A large polyethylene tube is then taped on the cheek, leaving about 2 cm. above, and the lower end is left long enough so that it can also be taped to the lower part of the cheek. This keeps the canal open and permits epithelization around the tube. Broggi [8] states that many substances have been used as indwelling conformers for the repair of severed lacrimal canaliculi. He prefers stainless steel wire, supplied as the stylet for hypodermic needles of No. 20 or No. 21 gauge. These wires are not uncomfortable for the patient; they can be wiggled back and forth daily and still held in place on the cheek. There is also much less tendency to cutting the canaliculus. Bergler [9] believes that indwelling tubes are not as good as forming a new canaliculus from the mucosa of the mouth. He takes a 14 by 9 mm. strip of mucosa, places it over a rubber tubing, and sews it in place. It is sutured into an opening in the sac, the other end leading into the conjunctiva. Papst [10] reports the follow-up on 26 cases, 14 months after Supramid tubing had been placed in the nasolacrimal duct. Postoperative acute dacryocystitis was seen in four cases. Nine cases had recurring stenosis, with inflammatory granulation tissue in some portion of the nasolacrimal system. In six cases the implants were lost in the nasopharynx, and eight cases had rather good results. The Supramid polyamide plastic used gave less than 40% good results. He feels that the unfavorable results are caused by a reaction of the tissue to the Supramid. His results with dacryocystorhinostomy are superior. Kleberger's [11] results with Supramid were similar to those of Papst. However, he had only 4 cases out of 20 with fairly good results. Both feel that the over-all results are poor and that the implanting of this plastic material is unphysiological. Jäger [12] describes a cannula which is used in the canaliculus. The cannula is supplied with a brush, which is used for cleaning the cannula.

Dacryocystorhinostomy.—Enciso [13] claims to have done 5,000 dacryocystorhinostomies and describes his technique, which is similar to the Dupuy-Dutemps operation. He states that in all 5,000 cases the operation was successful. Hefel,[14] on the other hand, has operated on 74 patients with this same procedure. Permanent success was achieved in 87.88%. He thinks that the operation is

easy enough for even the beginner to have good results. Stow [15] also favors dacryocystorhinostomy and discusses many of the methods of performing this operation.

LACRIMAL GLAND

Thaysen and Thorn [16] compared the secretion of the lacrimal gland with that of similar glands. Urea appears to be freely diffusible through the gland. This is also true of the sweat glands. The concentration of urea is the same in tears as it is in plasma, over a wide variation of values. Potassium is probably secreted, since it is present in greater concentration in the tears than it is in the plasma. This is also true to a less extent for both sodium and chloride. Sweat and saliva are both hypotonic as compared with the extracellular fluid and contain sodium in lower concentration than does plasma. The findings demonstrate that the concentration of sodium in the lacrimal gland is independent of lacrimation and would suggest that the lacrimal gland, unlike the sweat and salivary glands, does not reabsorb sodium from its secretion.

Viallefont [17] compares the salivary and lacrimal glands anatomically, physiologically, and pathologically. He notes the anatomical proximity of the nervous control of the secretions of the two sets of glands. As nerve regeneration occurs in lesions of the geniculate ganglion, the nerve fibers may enter the lacrimal gland, rather than the maxillary or sublingual gland. The result is the phenomenon of "crocodile tears" while eating. There are a number of diseases which produce marked changes in both the lacrimal and the salivary glands. Among these, Mikulicz' disease and Sjögren's syndrome are of particular interest. Morgan [18] concludes from pathological studies that Mikulicz' disease and Sjögren's syndrome are similar manifestations of a generalized disease entity.

Stow [15] points out that considerable care should be taken in extirpation of the lacrimal gland. He recommends that only the subconjunctival portion of the gland should be removed and that care should be taken not to sever the levator muscle. Complete extirpation of the gland should not be done except in cases of malignant neoplasm or severe infection, such as tuberculosis.

THE LIDS

Mandibulofacial Dysostosis.—Recently there has been much interest in this syndrome. While the first cases were probably reported about 1880, the best description was given by Franceschetti in 1944; thus the condition is termed the Franceschetti syndrome. Tranos [19] described two cases. The syndrome is characterized by (1) obliquity of the palpebral apertures, accompanied by coloboma and sometimes abnormal growth of eyelashes; (2) hypoplasia of the facial bones, especially the malar, the maxilla, and the mandible; (3) abnormalities of the external, the middle, and the inner ear; (4) large mouth, high palate, abnormal growth, and malocclusion of the teeth; (5) blind fistula between the mouth and the corresponding ear; (6) abnormal growth of hair on the cheeks, and (7) possible combinations of abnormalities of the face and the skeleton. Tranos describes several forms of the disease, while adding two cases. Dermoids or dermolipomas are common in the condition, as is congenital symblepharon. It is assumed that the syndrome is caused by congenital arrests of the primitive ectoderm. I have followed one such patient since 1936. She had marked dystrichiasis, which produced severe corneal scars. Her main problem over the years has been the extra eyelashes. Recently, I have seen a patient with two dermatolipomas in the lid and on the bulbar conjunctiva with congenital symblepharon so extensive that one of the lesions had to be cut to allow the tears to flow to the inferior puncta. There were no defects in the lashes in this patient. O'Connor and McGregor [20] described a case of what appears to be an incomplete Franceschetti syndrome.

Young [21] presents a case of a newborn infant with complete eversion or ectropion of the upper lid. As soon as the head presented at delivery, the exposure of the upper lid was evident. The fold of the upper lid, called the transitional fold, was so swollen that the

lid opening was completely obliterated. This transitional fold was the exposed conjunctiva. As the child cried, the conjunctival swelling increased. The child presented the characteristic stigma of mongolism. In a few days the conjunctival swelling began to decrease, but some slough of the conjunctiva occurred. The extensive conjunctival tissue was then removed, with the patient under general anesthesia, but the child died the following day. Ostriker and Lasky [22] saw a similar case. In their case, however, the eyelids returned to normal three weeks after birth. They were unable to find a cause for the eversion. Since the condition apparently occurs in mongoloid infants, it would be interesting to discuss the problem with our Far Eastern colleagues. It is possible that marked spasm of the orbicularis may cause the eversion of the upper lid, as was discussed in last year's review.

Rundle [23] discusses the spastic versus the paralytic types of lid retraction in Graves's disease. The spastic type is one in which the levator palpebrae superioris is involved. It is most evident on looking down and is commonly diagnostic of Graves's disease. The paralytic retraction is most evident on upward gaze. This type is more likely to be associated with the severe ophthalmic forms of Graves's disease.

Burns and Lacerations of the Eyelid.—These lesions have been the subject of considerable discussion in the past year. Schofield [24] reports 144 cases of burns of the eyelids. Fourteen were of first-degree burns; 80 were of second- and third-degree, and 50 were of severe, third-degree burns. Flame and flash burning by gasoline accounted for 110 of the 144 cases. The treatment may be divided into two parts: (1) immediate therapy, and (2) delayed plastic surgery. In all cases of immediate therapy for burns of the eyelid, protection of the cornea is paramount. When slough develops early, the entire area may be excised and replaced by new tissue. Immediate skin covering may be provided by a split-thickness skin graft. Every effort should be made to cover the raw lid surfaces completely. One must be prepared to graft and regraft the skin of the lid. The author prefers what is known as an "epithelial outlay graft." This graft is most useful in the severe burn cases, and several operations may be necessary. The "epithelial outlay graft" procedure consists mostly in preparing a much larger graft than appears to be necessary. This is particularly indicated in order to prevent contraction of the lids. Very large grafts are used to cover even relatively small defects. A total of 837 operative procedures were performed on the 144 patients. The late complications include notching of the lid margin, trichiasis, epiphora, lid margin irritation, and granulomata. The last-mentioned complications were particularly pronounced when skin and conjunctiva were joined. Symblepharon was not unusual. Five eyeballs in this series were removed because of exposure and drying, blinding from the subsequent infection, and severe corneal damage. The late results in this series are summarized as excellent, satisfactory, and fair. Excellent results were obtained in 20 cases (14%); satisfactory results in 87 cases (61%), and fair results in 37 cases (25%). The end-result depends always upon the severity of the burn, but equally important is the manner in which the burn is handled. Pritikin and Duchon,[25] contrary to most present-day opinion in the acute treatment of burns, treat most burns with lukewarm wet compresses of boric acid. They also discuss freezing, electric burns, and x-ray burns, which were not important in Schofield's series. They do, however, stress the infection which complicates the burn or trauma. Newell [26] and Boley [27] also discuss thermal burns of the eyelid with emphasis on the hazards of industry. Most of these burns are from molten metal and steam, but actinic burns are not uncommon.

Lacerations of the eyelid * require that the surgeon have an excellent knowledge of the anatomy of the eyelid before repair is attempted. Extreme care should be exercised in realigning the skin. Likewise, the direction of pull and repair of the orbicularis is

* References 28 through 32.

all-important. Callahan [31] wishes to stress that the repair should be done within 24 to 48 hours. Many of the procedures are complicated and do not lend themselves to reviewing. Some authors, such as de Saint-Martin,[32] think it is better to carry out a plastic procedure than a simple end-to-end anastomosis of the structures.

Minor surgical procedures on the eyelid follow general principles.† Incision, excision, fulguration, and electrolysis are commonly used for these minor procedures.

Bacterial Infections of the Eyelid.—Most ‡ of these infections are caused by the Staphylococcus, with the addition of other organisms. Very few additions have been made to last year's review.[4] Fazakas [38] says that favus is present in the upper and lower lid margin, but it must be a rare occurrence. He also points out that the actinomycosis group of organisms may produce a blepharomeibomitis.

King and Forrest [39] isolated the vaccinia virus from a case of vaccinia on the eyelid. They felt that chlortetracycline (Aureomycin) was effective in treatment. They state that while the untreated case runs a course of from 28 to 31 days, chlortetracycline was effective in 24 hours to 4 days.

Allergy of the Eyelids

Thomas [40] discusses the entire field of allergies in relation to all the structures of the eye and states that every structure in the eye may act as a shock tissue. He believes that dermatitis, particularly contact dermatitis, and atopic dermatitis are predominant. He also feels that blepharitis marginalis of the sicca variety and blepharitis ulcerosa may be either allergic or due to a bacterial sensitivity. He states that while styes or hordeola and chalazia may be acute, with pus formation, some are chronic and are of allergic origin. They are probably due to food sensitivities, but pollens may play an important role. Wolf [41] presents an interesting type of eczematous dermatoconjunctivitis which he feels is most frequently due to contactants. He presents a woman who was sensitive to nickels, or at least the metal used in making nickels. He states, "This is a true case of a person being broken out from money, if not with it." He stresses correct diagnosis, the detection and elimination of the offending agent, and avoidance of overtreatment.

Since allergies may produce edema of the eyelid, it is natural that Steckler [42] should discuss baggy eyelids. He enumerates the causes of baggy eyelids as (1) edema, which may be either essential or undetermined; (2) diminished muscle tone; (3) vasomotor stasis; (4) allergic responses; (5) atrophic changes in the epidermis or subcutaneous tissue; (6) familial traits, and (7) herniation of periorbital adipose tissue through the weak tarso-orbital fascia. He has devised a surgical procedure which consists mostly of removal of the skin of the lid but cautions, however, against overcorrection in order to avoid development of an ectropion. He also cautions against keloid formation, especially in Negroes.

Baggy eyelids may reach such proportions as to be called elephantiasis. Keidan [43] reports a case of an 8-year-old girl who received a bump on her forehead, causing a hematoma. The eyelid developed some discoloration, which faded in about three weeks, but a small swelling remained on her forehead. A few weeks later the lids recurrently began to swell, the swelling increasing with each attack. With one of these attacks, the patient was admitted to the hospital because the skin was bright-red and shiny and the temperature 103 F. This condition may have been an erysipeloid reaction. After penicillin was given and the inflammation had subsided, the skin remained edematous, producing an extensive elephantiasis.

Ocular Psoriasis.—Contrary to the opinion expressed by Vrabec and Pillat in last year's review,[4] Kaldeck [44] feels that ocular psoriasis is common. He found 11 cases of ocular involvement in 90 cases seen in his private practice, and he gives a short description of each of the 11 cases. In most of the cases the lesion consists of the silvery scales on the

† References 33 through 35.

‡ References 36 and 37.

lid border. However, one case had a plaque on the conjunctiva similar to the one reported by Vrabec. The ophthalmologist should be on the lookout for cases of psoriasis occurring on the skin of the lids.

Ptosis.— Blepharoptosis is a deformity of the upper lid with a strong hereditary tendency. It was classified in last year's review.[4] Piper [45] thinks that ptosis is an example of a decrease in the ocular function involving all of the extraocular muscles, at times including the pupillary reflexes. Pupillary changes are common, and the symptom, therefore, should be considered as one of general ocular weakness.

The surgery of ptosis follows very much the same pattern as that presented in last year's review, with some minor modifications.§ Caldemeyer [46] emphasizes the criteria for a perfect operation as follows: 1. The curve of the margin of the upper lid should overlap the cornea equally on the two sides. 2. The lid should be a smooth curve and similar in the two eyes, without notching. 3. The palpebral crease of the upper lid should correspond on the two sides. 4. The eyelids on both sides should close completely. 5. Normal winking should be possible. 6. The vertical distance between the eyebrow and the margin of the upper lid should be normal. 7. The upper lid should operate synchronously with the globe in all directions. 8. Diplopia should be absent. Vannas and Vannas [47] present a large series, 268 patients, on whom 327 ptosis operations were performed. The authors began doing the ptosis operation in 1912 and divide their cases into three groups: (1) the mild, (2) the severe, and (3) the severest. For the milder cases they present the Vannas operation, which in many respects is similar to that presented by Iliff.[48] It consists of removing a portion of the tarsus and suturing the levator and aponeurosis to the edge of the removed tarsus. Iliff removed the conjunctiva, whereas they prefer to leave the conjunctiva free. For the severer cases, Vannas and Vannas use the Eversbusch or the Blaskovicz operation, which they have modified somewhat. During the course of 20 years they performed the Blaskovicz operation on 165 patients. The results in this series are certainly gratifying. Iliff's procedure differs only in that he shortens the conjunctiva, Müller's muscle, and the levator tendon and reestablishes the filamentous attachments to the septum orbitale, without disturbing the anatomical relations of these structures. Both Iliff's and Vannas' operation should be successful in mild cases of ptosis. Leahey [49] presents a modification of the Friedenwald-Guyton suspension suture of the lid to the frontalis muscle. He uses a length of braided tantalum suture through a tantalum mesh, which is buried near the lid border and in the brow. When there is lid action, he prefers to do some type of surgery on the levator in 70% of his cases. He likes a modified Eversbusch operation. In an attempt to prevent lid notching, he uses three Frost sutures, instead of the usual one.

§ References 46 through 50.

Tumors of the Eyelids

The controversy between the advocates of surgical treatment and x-ray treatment for tumors of the eyelid continues.‖

Benign calcified epithelioma is certainly a rarity on the eyelid. However, two cases are reported.¶ Pathologically the diagnosis is comparatively simple, but clinically it is difficult. Increased vascularization of the skin over the tumor may bring it to one's attention. Zankan [51] feels that the skin redness is probably due to the irritative nature of the lesion. The authors also point out that it is commonest in women. Whenever a lesion is firm, yet feels cystic and is more vascular than usual, one should think of a calcified epithelioma. The treatment is of necessity surgical.

The report of an interesting symposium # compares x-ray and surgical treatment of malignant tumors of the eye and its adnexa. Miescher [53] presents 254 tumors in 226 patients. Two hundred one tumors (79.1%)

‖ References 51 through 61.

¶ References 51 and 52.

References 53 through 55.

were basal cell carcinoma; 46 were squamous cell carcinoma (18%), 6 (2.4%) were malignant melanoma, and 1 (0.4%) was a sarcoma. The author presents the dosage of x-rays used in treating most of the tumors and states there is little difference in the results whether the treatment is given all at once or in fractional doses. One hundred ten tumors were treated by a single dose, with 8 recurrences, while 122 were treated with fractional doses, with 32 recurrences. Most of the tumors recur in the first year.

Fig. 1.—Malignant melanoma. Reproduced from Miescher, G.: Ophthalmologica **127**:219 (April-May) 1954; published by S. Karger, Basel.

A reproduction of a malignant melanoma is presented in Figure 1, which shows a malignant melanoma before and after it was treated with radiation. The result is good. No cataracts developed in the group; however, skin telangiectases and pigmentary changes were fairly common. Entropion occurred in 4 patients, or 1.7%, and ectropion occurred in 14 patients, or 5.9%. Of the benign tumors of the lid, angioma is the most radiosensitive. Miescher uses mostly soft rays of 12 to 30 kv. for treating benign neoplasms. He feels that there are no hard and fast rules on x-rays versus surgery in the treatment of malignant tumors around the eyes. The surgical therapy was presented by Streiff.[84] Franceschetti, in discussing these papers on the problem of x-rays versus surgery said: "With a good x-ray therapist, the treatment by this method is probably the best. If the therapist is not so good, then use surgery." Werner[85] combines surgery and x-ray therapy. However, he divides his patients into three groups: those whose malignant tumors are superficial; those whose tumors are medium deep, and those whose tumor is deep with metastasis. In the first two groups, surgery or x-ray therapy will be effective. However, the third group requires radical surgery followed by x-irradiation.

Turner and McPherson[86] prefer surgery, reserving radiation for the patient who has a recurrence. They present four methods of resecting portions of the lid: The first is a simple resection of the tumor with a halving operation (also presented by Straeth,[87]) and is the simplest of the procedures. The second is a sliding graft, usually from the temporal area or a temporal flap. The third is the Hughes operation for removal of most of the lid, and the fourth is the type of operation described by McPherson in last year's review.[4] Smith[88] presents a procedure for rebuilding the lateral canthus by using a sliding temporal flap. Later the lid fissure is opened. Spaeth[89] likewise uses large temporal flaps to fill major defects after removal of large malignant tumors. Both these procedures follow surgical principles, and their results are excellent.

CONJUNCTIVA

Congenital Anomalies.—Congenital defects of the conjunctiva are extremely rare. A number of folds are sometimes seen in Franceschetti's syndrome, as are dermatolipomas of the conjunctiva. These dermatolipomas may be either in the lid or under the bulbar conjunctiva.[10] Folds involving the skin or the conjunctiva may extend either from the bulbar conjunctiva onto the lid to-

ward the inner canthus or toward a notch in the lid. Bose [62] presented a congenital angle band, which appears to be an epitarsus, but it is not related to Franceschetti's syndrome.

Metabolic Errors.—Goar and De La Motte [63] present two cases of cystinosis of the conjunctiva with rickets. The diagnosis was made by examination of the cornea with the biomicroscope, and in one case crystals were found in a stained preparation of excised conjunctiva. Whenever severe rickets is present, the ophthalmologist should examine the cornea or make a biopsy of the conjunctiva as an adjunct to diagnosis.

Hypercalcemia also produces changes in the cornea, conjunctiva, and sclera, as was shown by Walsh and Murray.[64] The changes produced by hypercalcemia can be most readily recognized in the cornea. However, they may be present in the conjunctiva, where moderate to severe reactions may occur. Walsh and Murray feel that they suggest phlyctenular conjunctivitis, and the authors believe that all cases of phlyctenular disease should certainly have a serum calcium estimation. Ophthalmologists should be alert for calcium deposits due to other causes. Calcium deposits have been reported in persons who have been on a Sippy diet for long periods because of gastric ulcers.[65] Some of these deposits may occur in the conjunctiva or the cornea.

Conjunctival Blood Vessels.—Of recent years there have been detailed descriptions of the bulbar conjunctival blood vessels in various disorders.* Landesman and coworkers [66] have continued their research and present the conjunctival vascular findings in the toxemias of pregnancy. Previously, they had reported mild spasm of the arterioles during the second and third trimesters of normal pregnancies. In some of these patients more changes were evident during labor, but these changes disappeared entirely during the first week post partum. In the toxemias of pregnancy, on the other hand, there is further progression of the conjunctival vascular changes visualized as compared with those in the normal pregnancy. The changes in the vascular bed in the toxemias appear earlier and are more advanced than those of the normal. These changes also occur earlier and are more advanced than those occurring in the retina. Spasm and ischemia increase with the severity of the toxemia and reach a maximum in eclampsia. Except for extensive renal disease, granularity of the vessels does not necessarily differentiate the normal from the toxemic patients. Tortuosity of the capillary beds is more consistently seen in severe hypertension and in severe preeclamptic states. After delivery these vascular changes persist for longer than a week, and sometimes for months, particularly in the hypertensive group. The vascular changes may not return to normal for six weeks or more. In the diabetic patients, particularly with toxemia, changes are also apparent. Capillary aneurysms of the conjunctiva were not seen in the present series. However, vesicular aneurysms and intravascular thrombi associated with hemorrhages were commonly observed in this group.

Ditzel [67] and associates tried to compare the normal blood vessels of the bulbar conjunctiva in children of diabetic mothers and those in children of normal parents. They compared 75 children of diabetic mothers with 75 of nondiabetic parents. They divided their patients into four grades, which they call Grade 0, with no change; Grade I, with swollen venules and minor irregularities in the capillaries, which take an angular course; Grade II, with considerably more capillary change and, in addition, conjunctival edema, and at times hyaline infiltration, and Grade III, with the capillary and the conjunctival changes, but also with marked alterations in the veins, consisting in elongation of the vein and granularity with hemorrhages and tortuosity. Of the children of nondiabetic mothers, 84% showed no changes in their conjunctiva, while only 23% of the children of diabetic mothers showed no change. In the children of the diabetic mothers the changes ranged from Grade III, 9%; Grade II, 24%, to Grade I, 44%. This group also

* References 4 and 66 through 68.

showed a higher incidence of prediabetes with the glucose tolerance test than did the children of nondiabetic patients. It is suggested that the abnormalities in the conjunctiva may be of pituitary origin.† Beetham, in discussing the paper, expresses concern that the ophthalmologists had not observed many of these changes. He suggests that the authors proceed with caution. Similarly, Givner [68] questions some of the vascular changes reported by several authors and points out that Adler has rightly said:

> The variations in the appearance of the capillaries and arterioles in the normal conjunctiva of man may vary from vessel to vessel so that caution must be observed in connection with changes found with a peculiar disease, or even for that matter interpreting them as indicating a disease state.

Givner insists that blood sludging and other conjunctival changes should be followed by ophthalmologists, for they are in a better position to judge these abnormalities. He presents a number of interesting cases.

Degeneration of the Conjunctiva.—Pterygium is the commonest degeneration of the conjunctiva, and it is the subject of a fascinating paper by Rosenthal.[69] Most of the surgical procedures for pterygium have been advocated, discarded, and readvocated over a period of many years. The first recorded pterygium operation apparently was done before 1000 B. C. There have been many types of surgery for pterygium, using sharp instruments, caustics, and other methods, such as electrolysis and irradiation. There is no uniformity of opinion as to the best form of therapy. Many modifications of pterygium therapy have been advocated. For example,[70] a window is cut in the sclera and the pterygium buried under the sclera. The anterior layers of the sclera at a distance of about 4 mm. from the limbus are incised, and a fistula is prepared so that the head of the pterygium can be buried into this cleft. Although other degenerative phenomena are not as common, Pico [71] presents a case of fibrotic hypertrophy of the plica semilunaris. The plica was so thickened that it suggested a new growth; a biopsy specimen was therefore taken. The material was composed of dense collagen with some edema. The author felt that it was a rare sequela of mild chronic conjunctivitis.

† Ditzel and associates have reported their findings in several other journals.

Conjunctivitis

Several interesting studies have been conducted. Noteworthy is one by Grünberger and Kofler,[72] who took cultures from the conjunctivas of 53 women immediately after delivery and compared these with the conjunctival cultures of the babies after birth, both before and after Credé's prophylaxis. In the mothers, Staphylococcus aureus was found 26 times, Staphylococcus albus 22 times, a Streptococcus 12 times, and Escherichia coli 21 times. The baby's conjunctiva was less likely to be contaminated than would be expected. However, staphylococci, of both aureus and albus types, were discovered in the conjunctiva, while streptococci and Esch. coli were rare. No difference was found in the organisms present in the conjunctiva whether Credé's prophylaxis had been used or not. Streptococci and Esch. coli may have been a little more numerous after Credé's prophylaxis than they were before. Cultures were obtained on the second and fifth days of life.

Duszynski [73] compared the techniques of obtaining material from the conjunctival sac for cytologic examination. None of the subjects he used complained of any difficulty with the conjunctiva, and there was no apparent pathological process in the conjunctiva. The intent of the examination was to demonstrate the cytology of the normal conjunctiva. Material was gathered by three methods, namely, (1) with a dry swab, (2) with a wet swab, and (3) by scraping with hard-composition fiber material. This material was then placed on a slide for examination. Dilute Giemsa stain was used. The author found that the wet- and dry-swab techniques were superior to the scraping method in obtaining cellular material for microscopic study. An average of 68.9 cells were found on each slide, of which 71% were

epithelial cells and 24.5% were polymorphonuclear leucocytes. The author concluded that the dry-swab technique of taking smears was the easiest to study and yielded the most information.

Cason and Winkler [74] compared the preoperative cultures in their group of 1,604 patients with the figures of Khorazo and Thompson. Micrococcus pyogenes var. albus and diphtheroids were recovered in culture more frequently than any other organism. M. pyogenes var. aureus was recovered from the lid in 95% of the patients and from the conjunctiva in 68%. The frequency with which certain Gram-negative bacilli were encountered is greater than heretofore recorded. These organisms, members of the enteric Gram-negative rod group, were cultured from the conjunctiva of 5% of the patients and from the lids of 7%. It is interesting to note that in Khorazo and Thompson's studies only 1.6% of the conjunctival cultures contained Gram-negative bacilli. The organisms were mostly unidentified Gram-negative rods. Diphtheroids were common in the present series, accounting for 40% of positive cultures from the lids and 33% from the conjunctiva. Only 23% of the conjunctival cultures (374) showed no growth. Only 3% of the lids (45 cases) showed no growth. The increase in the cases of Gram-negative rods is certainly noteworthy.

Halbert and co-workers ‡ have shown that many strains of bacteria found in the normal flora of the eye are antibiotic-producing bacteria. From a series of 22 organisms which produced antibiotics, 9 different antibiotic agents were found. Fourteen [76] of the 22 organisms were rather clearly a polypeptide, as evidenced by their destruction by enzymes. There were eight, however, which were resistant to enzyme activity but still appeared to be of a peptide structure. The antibiotics produced were most effective against Micrococcus, Corynebacterium, Sarcina, and some bacilli. The antibiotic producers were found among 280 patients; of these, the conjunctiva appeared normal in 203, while 156 patients showed some kind of conjunctivitis. Thygeson and I have both studied many of the cases of conjunctivitis from the same institution as did Halbert, and, while we were able to find a few cases of trachoma, Halbert [75] and his co-workers did not. There is certainly clear agreement that mongoloid patients show clinically an increased amount of conjunctivitis, for 34 out of 44 cases (77%) had conjunctivitis, while only 67 of the 215 nonmongoloid patients (31%) had conjunctivitis. It is interesting that those persons with diseased conjunctivae had a higher incidence of active antibiotic-producing strains in their conjunctiva than did normal persons. The role of the antibiotic producers in conjunctivitis has not as yet been definitely determined. It is possible that these antibiotic producers may be more active on the culture plate than they are in the tissue.

Leopold [77] presents an interesting bacteriological study in which the eyes of rabbits were inoculated with known organisms and attempts then made to recover the organisms. The anterior chamber, the iris, the vitreous, and the cornea were also inoculated. Later, at various intervals, attempts were made by cultural methods to recover the organisms. The experiments showed that the anterior chamber and the cornea have a definite natural resistance to infection. A positive culture, however, in these cases was always easily obtained from the vitreous, even though cultures from the anterior chamber failed to grow micro-organisms. This certainly follows my personal clinical and bacteriological observation in that it is rare to get a positive culture from the anterior chamber, whereas a positive culture can almost always be obtained from the vitreous in cases of intraocular infection. In discussion of this paper, Dr. Walsh made the comment that 90% of postoperative infections were due to the Staphylococcus. This was not the experience of Winkler and Cason,[78] who state:

> Reports of infection following cataract extraction, have, in the past, incriminated M. pyogenes var.

‡ References 75 and 76.

aureus (Staphylococcus aureus) as the commonest etiological agent. While the present series of 1,653 extractions is not unduly large, it is of interest that when infection did occur, M. pyogenes var. aureus was found to be the cause in only one case. Instead, Gram-negative rods belonging to the so-called enteric group of bacilli were involved, with A. aerogenes and Ps. aeruginosa the commonest offenders. P. vulgaris; also a member of this general group, was recovered in one case.

Gram-negative rods have likewise caused more postoperative infections in our small series than has the Staphylococcus.

Allergies of the Conjunctiva

There has been a great deal of discussion concerning the allergies of the lids and the conjunctiva.§ Some investigators are extremely enthusiastic,[80] while others [85] wish to identify the allergens. Theodore [79] has continued his interest in the subject and tries to explain allergy on the fundamental antigen-antibody philosophy. The author states that many foreign substances can act as antigens and includes physical influences, such as light, heat, cold, and emotional factors as possible allergic agents. It is convenient to divide the allergic reactions into two types, the immediate and the delayed. The immediate reaction occurs usually in a few moments, or certainly within an hour. This is the typical urticarial response, and here typically circulating antibodies can be demonstrated in the serum and may be transferred passively. The delayed type of response takes from 24 to 48 hours to develop and is typified by the eczematoid reaction. Much of this material was covered in last year's review.[4] It is interesting to note that Cosgrove [82] gives a clinical classification of the allergies, dividing them into the palpebral and the bulbar types. The palpebral types are (1) angioneurotic, (2) blepharitis, (3) follicular, and (4) a type that he calls "band," consisting of a red band in the inferior fornix. Under the bulbar type he classifies (1) episcleral and (2) limbal allergy and (3) keratoconjunctivitis. He makes the interesting observation that glaucoma was found in 14 of his patients, all of whom had the palpebral types. All the cases of glaucoma were in patients over 45 years of age. He does not feel, however, that the treatment of allergy is very effective, although he reports 63% of all his cases of allergy as being successfully treated, while 35% had recurrence regardless of treatment. Lemoine [81] stresses the emotional factors in the development of allergies. He also notes that certain foods, tobacco, alcohol, and refined sugars may exaggerate the allergic reaction in some persons, and he makes the interesting observation that one of his patients developed dendritic ulcer of the cornea every time she ate chocolate.

Therapy of all types of allergic conjunctivitis varies widely, from nonspecific therapy, using antibiotics and other substances, to desensitization techniques and use of hormones. Hydrocortisone and cortisone are widely used. It is of interest that Solotorovsky and Winsten [84] state that cortisone does not inhibit active or passive anaphylaxis in the guinea pig, but it does inhibit anaphylaxis in the mouse, the degree of protection against anaphylaxis being directly related to the dose of cortisone. Hanser [86] also has shown that the use of cortisone produces a drop in the eosinophile count in smears from the conjunctiva.

Phlyctenular keratoconjunctivitis is almost always an allergic reaction to tuberculoprotein, according to Thygeson,[87] although on rare occasions it may be an allergic reaction to bacterial, viral, or fungal infection. Thygeson states that numerous authors feel that the Pneumococcus and the Koch-Weeks bacillus may be associated with phlyctenulosis in children. He feels, however, that these two organisms are low sensitizers and that they may act as a trigger mechanism to produce the sensitivity to the tuberculoprotein. He presented five cases of tuberculosis-free phlyctenulosis in which he believes that the sensitizing agent was the Staphylococcus. All were improved on the elimination of the staphylococci and desensitization with Staphylococcus toxoid. He also states that

§ References 79 through 85.

phlyctenulosis may be produced by a sensitivity to Candida albicans and to the lymphogranuloma venereum virus, while Coccidioides was probably the sensitizing agent in two cases.

Acne rosacea involves the lids, the conjunctiva, and the cornea. Goldsmith [88] states that the commonest ocular manifestation of rosacea is blepharitis, which consists of a scaly desquamation of the skin around the lash follicles, associated with dilatation of the superficial skin vessels. Chalazia and styes may be present. The patients, of course, have seborrhea. The blepharitis improves as the skin condition improves. The second ocular complication is a diffuse hyperemia of the conjunctiva, frequently associated with the blepharitis. The conjunctivitis may run concurrently, with small marginal catarrhal ulcers which resemble those of true rosacea but are not identical. It is the type that is associated with staphylococcal infection of the conjunctiva. Nodular infiltrations of the conjunctiva, with or without episcleritis, may also occur; however, these complications are not common. The nodules develop in the exposed interpalpebral region near the limbus. They are surrounded by dilated vessels and in many respects resemble the conjunctival phlyctenular disease. The author does not believe that staphylococci and diphtheroids are of any importance in the etiology of acne rosacea but says that they are commonly found. The presence of the staphylococci may suggest an allergy to Staphylococcus toxin. He also discusses the possibility of an endogenous allergy to the patient's own hormones, which has previously been suggested by Zondek. The seasonal variation in the disease may be influenced by photosensitivity. In treatment, the author favors roentgen therapy. Cortisone, however, is widely used.

Borrie [89] reviewed 130 cases of cutaneous rosacea, in 99 of which there were ocular lesions. He concluded that the ocular lesions were relatively commoner in men and that 53% of the cases had cutaneous lesions occurring before the ocular lesions and only 20% had ocular lesions occurring before the cutaneous lesions. He states that the keratitis is the commonest ocular manifestation and that blepharitis and sebaceous changes are not very common in rosacea. It has been my experience that the blepharitis is the commonest disorder.

Unusual Allergic Manifestations.—O'Brien and Storey [90] present an interesting patient who was receiving gold injections for the treatment of his arthritis, with but little improvement. Blepharokeratoconjunctivitis developed while he was on phenylbutazone therapy. The sensitization progressed to the development of a generalized hypersensitivity reaction to the drug. The postmortem findings showed a hypersensitivity reaction, which was described as of three types; polyarteritis nodosa, hypersensitivity angiitis, and granulomatous lesions. Steel and Moffatt [91] presented a case of the Stevens-Johnson syndrome with granulocytopenia, occurring after treatment with phenylbutazone. While this case is similar to the one previously described, the patient recovered. In this case a reaction could be provoked by even a small dose of the substance. The authors stress that one should be extremely cautious in advising or prescribing phenylbutazone where there is a past or a family history of allergy.

Oculocutaneous lesions continue to be of importance,‖ but no new findings have been presented since last year's review. Systemic administration of cortisone and corticotropin is considered the best form of therapy.[93]

Unusual Forms of Conjunctivitis

Kall,[95] in observing the protozoan conjunctivitis that occurs in Denmark, thinks he has demonstrated a nematode in hanging-drop preparation and in biopsy specimens from the conjunctival tissue.

Ophthalmologists should be on the lookout for common warts of the eyelid producing conjunctivitis, as has been demonstrated by Mattsson.¶ Seven of his patients had catar-

‖ References 92 through 94.

¶ References 96 and 97.

rhal conjunctivitis. There was no keratitis. All the cases were obviously caused by one or more common warts on the lid border. While it has been stated that the location of the wart is most important, Mattsson says that the size of the wart determines the degree of severity of the conjunctivitis.¶ Keratoconjunctivitis is apparently common in some of the artificial silk factories, according to Karsch.[98] He says that the conjunctivitis is due to the H_2S or carbon disulfide, which acts, together with hydrogen sulfide, as an irritant. It causes this effect because of the drying. The tears are not sufficient to wash the material out of the eye, and therefore a keratoconjunctivitis is produced. The best prevention is ventilation of the room.

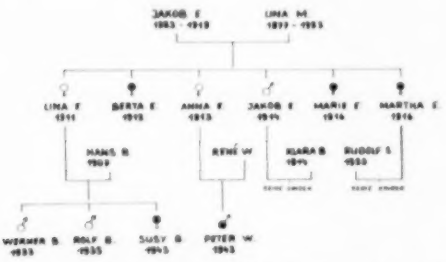

Fig. 2.—Pedigree of familial pseudomembranous conjunctivitis. Reproduced from Goldmann, H., and Hof, W.: Schweiz med. Wchnschr. **84**:73 (Jan.) 1954; published by Benno Schwabe & Co., Basel.

Pseudomembranous conjunctivitis was discussed in last year's review,[4] the French authors suggesting that it was a familial disease. Goldmann and Hof [99] present the family tree of this familial pseudomembranous conjunctivitis. The family tree is reproduced in Figure 2. The pseudomembranous conjunctivitis followed sore throat, vulvovaginitis, and acute nephritis. The family history showed that three aunts and one cousin had suffered from this disease. Two of these persons were completely blind, and one was almost blind. The authors feel it is not so much a family carrier state as a familial deficient defense mechanism that is important. This disease develops during the first decade of life and is commoner in females than in males.

Cat scratch fever is discussed in an interesting editorial in *The Journal of the American Medical Association*,[100] in which the opinion is expressed that the original lesion is in many cases a conjunctivitis, followed by a regional lymphadenopathy, and at times a generalized lymphadenopathy. In a personal communication, Cassady states that there is a strong similarity between the patients who had Leptothrix infection and those with the so-called cat scratch fever of Daniels and McMurray.[4] Cassady retested many of his former patients who had had the Leptothrix infection and found that they were sensitive also to Daniels and McMurray's antigen. Since the Leptothrix also occurs in cats and can frequently be transmitted to humans, as was demonstrated by Henry,[101] the two infections may be one and the same disease. I feel that Verhoeff's and King's procedures should be applied to patients with so-called benign infectious lymphoreticulosis to determine whether the Leptothrix is present in cat scratch fever. The ocular manifestations in infectious mononucleosis are presented by Tanner [102] in a paper which substantiates some of the evidence presented by Jones, Howie, and Wilson.[4] Tanner believes that there are two types of ocular manifestations: (1) involvement of the eye and the adnexa directly with the infectious agent of infectious mononucleosis, and (2) the effect upon the vision and the neuro-ophthalmic apparatus, apparently due to more remote lesions. The latter lesions are probably in the central nervous system. The direct ocular involvement is probably fairly common; at least Jones, Howie, and Wilson felt that it was, since 84 of their patients had acute conjunctivitis. Tanner believes that there is potential seriousness associated with the lesion, particularly when the central nervous system is involved. He emphasizes that the widespread distribution of the lesions of mononucleosis is not fully appreciated. He states that conjunctivitis, orbital edema, retrobulbar pain, optic neuritis, retinal edema, and uveitis may occur. Laboratory tests may be of value in

making the diagnosis, and the finding of the typical cells of infectious mononucleosis in the blood stream is also of great aid. Jones and associates [4] describe the finding of characteristic mononucleosis cells in the conjunctival biopsy tissues.

Cüppers and Krücke [103] discuss the problem of para-amyloidosis of the eye. While amyloidosis may occur locally in the conjunctiva without any other involvement, it may also be the first manifestation of generalized amyloidosis. The authors feel that there is always a connection between the local and the generalized para-amyloidosis. The eye may also be involved in generalized para-amyloidosis. The para-amyloid is usually deposited around the vessels in the uvea and in the sclera and is frequently also deposited around the iris vessels, so that the pupil will not react to light. Amyloid may also be deposited in the interstitial tissue of the extraocular muscles and is sometimes found in the optic nerve. In generalized amyloidosis the conjunctiva may be spared. The accompanying chart may help to visualize better the development of para-amyloid.

Paraprotein Formation

Transudation into tissue	Paraproteinemia	Paraproteinuria
Storage of paraprotein in tissue	Paraproteinemic nephrosis	
Paraproteinosis		

VIRUS DISEASES

Sanders and his co-workers [104] have critically reviewed the literature on cultivation of viruses and have divided the known viruses into three groups: Group I, viruses which have been propagated in tissue culture (all criteria have been met); Group II, viruses which have doubtfully or temporarily been propagated in tissue culture (one or more criteria have not been met), and Group III, viruses which have not been propagated in tissue culture.

Group I: Viruses which have propagated in tissue culture (all criteria have been met)

Coxsackie	Measles
Encephalitides	Mouse encephalomyocarditis
Japanese B encephalitis	Col-SK
St. Louis encephalitis	MM
West Nile encephalitis	Mouse encephalomyelitis (Theiler's GD VII virus)
Semliki Forest fever	Mumps
Russian spring-summer encephalitis	Newcastle disease
Eastern equine encephalomyelitis	Poliomyelitis
Western equine encephalomyelitis	Pseudorabies
Venezuelan equine encephalomyelitis	Psittacosis
Foot and mouth disease	Rabbit myxoma
Fowl leucosis	Rabies
Fowl plague	Rous sarcoma
Herpes simplex	Rift Valley fever
Hog cholera	Vaccinia
Influenza	Variola
Lymphogranuloma venereum	Vesicular stomatitis
Lymphocytic choriomeningitis	Virus III
	Yellow fever

Group II: Viruses which have doubtfully or temporarily propagated in tissue culture (one or more criteria have not been met)

"Anopheles A and B"	Rabbit fibroma (inflammatory strain)
Avian encephalomyelitis	Fowl pox
Common cold	Infectious hepatitis
Ectromelia	Louping ill
Ilheos	Sheep pox
Epidemic keratoconjunctivitis	Varicella

Group III: Viruses which have not propagated in tissue culture

Herpes zoster	Sandfly fever
Inclusion blennorrhea	Teschen's disease
Infectious mononucleosis	Trachoma
Rabbit fibroma (fibromatous strain)	

HERPES SIMPLEX

Thygeson [105] has observed an extraordinary increase in the number of cases of primary ocular herpes in which the severe conjunctivitis and preauricular lymphadenopathy resemble the changes seen in epidemic keratoconjunctivitis. I have also observed a larger number of patients with acute herpes infection of the conjunctiva, particularly in youngsters. Ophthalmologists should be alert to this disorder.

It is interesting to report the findings of McNair Scott and his co-workers,[106] who devised a method wherein rabbit corneal epithelial cells were grown in tissue culture and were infected with herpes simplex virus. A comparison was made of the histological changes observed in the infected cells and the amount of infectious virus detectable in the tissue at various hours after infection. The histological changes reveal that during the latent period, which lasts from two to

six hours, when infectivity is low, alterations occur in the nucleus which indicate a profound disturbance in its structure. After this lag phase, there is an increase in the infectivity of the virus, which takes place in from 6 to 12 hours. The nuclear structural changes then become differentiated into a full-formed inclusion body.

It is interesting to speculate on the fate of viable herpes simplex virus that is administered intravenously in man. Geller and his co-workers [107] injected large amounts of viable egg-adapted strains of herpes simplex virus intravenously in 12 volunteers and then attempted to recover the virus by the egg technique. No virus could be recovered from the blood. It is of interest that a complement-like heat-labile substance was demonstrated in the plasma of one patient. While neutralization tests in all the patients exhibited wide variations in the titer, the intravenous injection resulted in significant rises in titer in four out of the nine persons.

Epidemic Keratoconjunctivitis

Epidemic keratoconjunctivitis is still being found.# Eye clinics appear to be an important source of the infection. Cockburn and co-workers [108] reported on an interesting survey of a small epidemic. During the two months' period in which the study was undertaken, approximately 40 patients with glaucoma attended the eye clinic. Nine of these patients developed the disease (an attack rate of 23.5%). It was most likely that the inoculation occurred at some time during the examination for glaucoma, the tonometer being considered the most likely vehicle of transmission. Some of the patients from this eye clinic wandered into other clinics and smaller outbreaks occurred, so that six small epidemics were found, all centering around a single large eye clinic. Serological studies of serum from patients in the two epidemics were entirely negative for both St. Louis encephalitis and the so-called Sanders EK virus. Further inoculations may have been prevented by adoption of a more efficient method of sterilizing the tonometer. There is no doubt that this condition was an epidemic keratoconjunctivitis, since the majority of the patients developed corneal opacities and the disease ran a fairly typical course. Feist [110] made some interesting observations on the corneal changes associated with epidemic keratoconjunctivitis. He divides the corneal changes into four stages: (1) loosening of the epithelium, (2) protrusion of the epithelium, (3) typical foci of infection, and (4) incrustation or formation of denser opacities.

Greeley Disease

Cockburn [111] describes an epidemic of conjunctivitis associated with pharyngitis, muscle pain, and pyrexia. There is moderate follicular inflammation, without purulent discharge. There may be slight edema. There is very little discomfort or photophobia. The conjunctivitis persists for three days to three weeks. With the slit-lamp microscope, he found a few white plaques, 1 mm. or less in size, in the subconjunctival region. There was no ulceration. The throat lesions consisted of soft vesicles varying from pinhead to pea size, mostly on the soft palate. He was able to find 206 cases. All the patients were seen in the latter part of July and the first part of August, and nearly all of them attended a swimming pool in nearby Greeley, Col. He states that the disease is transmitted either by direct contact or by association with the swimming pool. Two other epidemics were followed, one in Missouri and the other at another place in Colorado.

Trachoma

I have reviewed more than 60 articles on trachoma,* and I find still a wide variation in opinion. The incidence of trachoma varies throughout the world.[112] Lindner states that trachoma has largely disappeared from Austria in the past 40 years. Better hygienic conditions may be of importance. An occasional patient with trachoma is found in London.[113] Amies and co-workers [114] claim that trachoma exists in the South African Bantu, even though follicles occur in many

References 108 through 110.

* References 112 through 171.

types of conjunctivitis and vascularization is sometimes seen with vitamin deficiencies, etc. Stages I, II, and III trachoma occur in children in the South African Bantu. They examined 109 children and found Halberstaedter-Prowazek inclusion bodies in 25 (23%). Of the 109 children, 74% had exudative conjunctivitis; 64% had Koch-Weeks infection, and 11% had influenzal infection. The photographs of the inclusion bodies are convincing. The authors found trachoma in patients from 1 year up to 8 years of age; however, the highest incidence was between the ages of 5 and 9 years. After 9 years of age the disease remained stationary. They examined a random sample of children and found 38 in whom pannus without scarring would indicate that healed trachoma was present. Herbert's pits were also found in Negroes.[115] Trachoma has been reported from Viet-Nam,[116] where the incidence is still very high and accounts for 80% of the clinic patients; from Papua and New Guinea[117]; from Podrigne,[118] and in Europe and the Far East.[119] A school has been set up in Casablanca, where 700 children are treated.[120] In one district in Tunis, from 85 to 92% of the population has trachoma. The great proportion of the patients have never been treated.[121] The incidence of trachoma is decreasing in Greece.† On the Fiji Islands the Hindus and the Chinese have trachoma, but during the war against Japan many of the native soldiers developed the disease; later, many of the native school children were found to have trachoma.[124] Trachoma is still prevalent in Egypt,[125] but this should not prevent trachoma patients from traveling from one country to another,[126] since the therapy is excellent. Lyons[127] thinks that the Koch-Weeks or the Gonococcus infection occurring in children in Europe eventually leads to trachoma, and he would like to prevent contamination of the child by the mother. He feels that combating these bacterial infections would be the most effective way of fighting trachoma. Busacca[128] summarizes all the changes that occur in trachoma histologically and clinically. This summary is an excellent one and should be read by everyone interested in external diseases. The pathogenesis and classification of trachoma continue to follow along the lines of MacCallan,‡ with minor variations.

Ching[134] would like to change the classification and presents two types of trachoma. First is a true, simple trachoma (a mild, insidious disease, frequently self-limited, and not especially infectious). It is a comparatively harmless disease, which involves the conjunctiva and the corneal epithelium. The second is an infectious or infected trachoma; the result of the addition to the trachoma virus of one of several secondary bacteria. It is the latter type that has been confusing everyone for the last 100 years, since the secondary infections will all vary. Ching presents an elaborate diagnostic sheet.

The etiology of trachoma still covers a wide variety of causes, while the major number of authors feel that it is a virus disease.§ Kirisawa[139] and Poleff‖ claim to have grown the virus of trachoma in tissue culture. Mitsui and co-workers[141] have demonstrated a toxic substance present in the tarsus that will produce a conjunctivitis when inoculated on the conjunctiva.

Tsutsui[142] presents an interesting study on the immunity which develops to trachoma and feels that this may be one reason for the development of chronic trachoma. He was able to infect himself three times, twice in the right eye and once in the left eye. A fourth attempt failed to infect the eye; however, a month later the right eye could be reinfected and acute trachoma developed. The degree of infection is dependent upon the number of inclusion bodies present, and they gradually disappear. He feels that there was a substance in his own serum which would attenuate trachoma. The local immunity being short-lived, while a general immunity is possible, it may be that the disappearance of the trachoma virus in chronic trachoma is an effect of immunity.

† References 122 and 124.

‡ References 129 through 133.

§ References 135 through 142.

‖ References 137 and 140.

Tavolara [143] presents an interesting corneal dystrophy occurring in trachoma which he thinks is Salzmann's dystrophy.

Surgery in trachoma continues to hold the major spotlight.¶ Chams [152] presents a beautifully illustrated paper, containing a great deal of information on the electrocoagulation treatment of trachoma. The colored pictures, before and after treatment, are well prepared and reproduced. He performed electrocoagulation on over 200,000 people! Most of the therapy is for trichiasis, ectropion, and entropion and was discussed last year.[4]

Medical Therapy of Trachoma.—Most of the reports on chemotherapy and antibiotic therapy were on the sulfonamide drugs and the wide-spectrum antibiotics. One of the best-controlled experiments on therapy was reported by Chastain and Newlin.[153] They treated 45 adolescent Navajo Indians. The patients all had Stage II or Stage III trachoma with entirely negative smears for secondary infection. Patients with early Stage II trachoma and Stage I trachoma, while treated, were not included in the paper because of the possibility of confusion with other ocular infections. Only patients with unmistakable pannus formation were included in the group. Chloramphenicol was given, 1 gm. being injected intramuscularly daily. No local therapy was used. The other group of patients was placed on sulfadiazine by mouth, ½ grain (0.032 gm.) of the drug per kilogram of body weight every 12 hours. In this group, sodium sulfacetamide, 10%, was used locally. While the patients were chosen at random, one patient who was sensitive to sulfonamides was given chloramphenicol. Twenty-six patients were treated with sulfadiazine, with a good response obtained in 22, or 84%. Twenty-one patients were treated with chloramphenicol. The treatment was highly successful in that symptoms improved in 24 to 48 hours and subsided entirely in from 3 to 4 days. An average of nine injections appear to be sufficient to eradicate the disease. The 4 patients who did not respond to sulfonamides were subsequently treated with chloramphenicol, making a total of 25 patients thus treated with chloramphenicol intramuscularly, with no additional local therapy. While the authors state that this treatment was most successful, the follow-up period has not been long enough to permit complete evaluation.

Streptomycin, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and the sulfonamides are all reported as effective in varying degrees.# Thygeson [171] discusses the criteria of cure in trachoma. He states that in a study of 130 trachomatous patients treated with the sulfonamide drugs, or topically with oxytetracycline, the disappearance of corneal lesions, including superficial infiltrates and corneal epithelial roughening, proved to be a valuable sign to the indication of healing. He feels that there is a lag in the absorption of the trachomatous conjunctival infiltrate, particularly the follicles. He feels that treatment should be stopped as soon as the cornea is cleared. A provocative test with cortisone appears to reactivate the virus. The virus was reactivated in four of seven cases of trachoma in which activity was in question. The reappearance of inclusion bodies in the scraping was followed by clinical signs of activity in three of the four patients. Thygeson does not believe that trachoma produces any immunity; however, it may heal spontaneously. It may lie dormant for long periods of time and can be reactivated by trauma or superimposed infection.

IMMUNITY

While immunity is not completely understood, recent research may be of help in understanding some of the methods whereby immunity develops. It has been said that immunity and hypersensitivity are closely allied, since they are both associated with antibody formation. Recent research * would indicate that there is no doubt that immunity develops in the lymph nodes and that lymphoid tissue is extremely important for immunity to develop.

¶ References 144 through 152.

References 154 through 170.

* References 172, 173, and 174.

Harris and co-workers † injected dysentery bacillus into the footpads of rabbits and then removed the regional lymph nodes. These lymph nodes were teased, washed, and then injected into normal animals. Antibodies then developed in the donor animal. When the antigen was injected into the footpad, the regional lymph nodes contained the highest titer of antigen, while the spleen contained lower titers. If the antigen was injected intravenously, however, the spleen contained the highest titers. Hale and Stoner[174] were able to grow both lymph node and spleen in the anterior chamber of mice eyes. Both produced antibodies, which could be easily detected in the anterior chamber. If skin was used instead of lymph node, then no antibody was detectable. These findings open a large field for investigation in the conjunctiva and develop from chemical or pharmaceutical preparations, as well as inflammatory materials.[175] Do the follicles play any part in the development of immunity?

TUMORS OF THE CONJUNCTIVA

Squamous cell epitheliomas may occur on the conjunctiva. Usually they occur in the bulbar conjunctiva.‡ As a rule, they are of low-grade malignancy and respond to surgery [176] or x-ray treatment.[177] Boase [178] found a patient with a lump between the cornea and the semilunar fold. It was removed, and the pathological report was that of an adenoma of the lacrimal gland. Of the conjunctival tumors, melanoma and melanosis of the conjunctiva [179] appear to be the most frequent.

† References 172 and 173.
‡ References 176 and 177.

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Correspondence

NEW PREPLACED CORNEAL SUTURE

To the Editor:—On page 129 of the ARCHIVES for July, 1954, is an article by Abraham J. Lanchner, M.D., entitled "A New Preplaced Corneal Suture." At the end of the article is a solitary reference to S. Baldino, who is credited with having devised a suture technique of a somewhat similar character.

If Dr. Lanchner consults the *Acta concilium ophthalmologicum*, 1950, Vol. 2, p. 1090, he will find a suture technique of a character exactly similar to that which he describes as new.

I have used this method now for several years and have every reason to agree with his statement that it "has certain advantages over other sutures."

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Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Truman L. Boyes, M.D., *Chairman*

Charles A. Perera, M.D., *Secretary*

Regular Meeting, April 19, 1954

Cyclodiathermy for the Treatment of Glaucoma. Dr. Ramon Castroviejo.

Cyclodiathermy is valuable in the treatment of all types of glaucoma which are not controlled by miotics or which show diminishing visual fields even when the intraocular pressure seems under control. The technique of cyclodiathermy was described, using 1.5 mm. penetrating pins, placed 5 to 5.5 mm. behind the limbus. The electrocoagulating current is held on 10 seconds for each application. Four applications are made in each quadrant. Ordinarily, eight applications are made. The full, or maximum, dose is 16 punctures. Phthisis bulbi is a rare postoperative complication. Glaucoma in diabetic patients and in the presence of active uveitis does not respond favorably.

DISCUSSION

Dr. Milton L. Berliner: To me, the story of cyclodiathermy for glaucoma presents one of the paradoxes in ophthalmology. Examination of the literature shows that the inception of the idea for this procedure can be traced back over 72 years (de Wecker and Masselon, 1882). I found almost 140 papers on this subject in the literature. The paradox lies in the fact that for the number of workers who praised it there was an almost equal number who condemned it. However, during the last few years, especially in European countries, more and more ophthalmologists have adopted it, and more and more are becoming enthusiastic concerning its value. I have observed this trend personally in my yearly visits abroad. In order to understand the reasons for the previous diversity of opinion, I looked through the records of cases of cyclodiathermy performed in the past at the New York Eye and Ear Infirmary. It soon became obvious that the story paralleled that in the literature before 1949. The following features were evident.

1. The operation was performed in small numbers by many different surgeons.

2. A variety of techniques were employed. Diathermy and electrolysis treatments, surface and penetrating, were given anywhere from 2 to 14 mm. behind the corneal limbus. There was no uniformity in the areas treated, the size or length of the needle, the temperature, the time (5, 7, 9, or 10 seconds), or the strength of the dose applied.

3. The procedure was relegated for the greater part to use in eyes in a hopeless condition, such as absolute, hemorrhagic, or secondary glaucoma, or in long-standing cases of chronic glaucoma in which several unsuccessful surgical procedures had been tried previously. Apparently, the original idea in this procedure was to produce a direct atrophy of the secretory portion of the ciliary body. In eyes in which blockage is complete and stasis has existed for a long time, the possibility of obtaining any return to a semblance of normal physiology is hardly possible. In many such cases the amount of treatment required just to reduce the pressure would be equal to the amount that would result in atrophy to the globe. This might be desirable if one wished to relieve pain in a blind eye; but, in my opinion, enucleation is far more rational.

In 1932 Weve noted reduction of pressure in the eye for long periods following diathermy treatment of retinal detachment. Weeker, in 1948, used a technique

similar to the one now advocated. After retrobulbar anesthesia he employed a flat electrode for surface treatment without conjunctival dissection—5 to 7 mm. from the corneal limbus in the corners between the insertion of the rectus muscles. He advocated a temperature of 90 C. for 10 seconds. This is similar to the present technique advocated by Castroviejo, except that the latter uses a perforating electrode 1.5 mm. in length for 10 seconds. I have followed Castroviejo's technique in my series, except that I ordinarily apply the diathermy current for seven seconds. This current approximates 35 to 40 ma. This setting cannot be a constant on the high frequency diathermy machine, since the patient is part of the circuit and the resistance of the patient varies in every case. Experience as to the ease of penetration with the needle should determine the further adjustments on the control dial in each case. The concept in the treatment, in my opinion, is not to affect the secretory portion of the ciliary body directly, but, rather, to influence it indirectly, by means of the ciliary nerve plexus. This nerve plexus, containing numerous ganglion cells, is found in the region 6 to 7 mm. from the limbus. The ganglion cells decrease in number as one goes anteriorly. None are found in the iris. By production of a trophic disorder in the plexus, inhibition of secretory activity occurs —a sort of surgical Diamox. That some trophic disorder occurs can be emphasized by the finding of a slight amount of corneal anesthesia in corresponding treated areas. Some vasomotor effect is added to this.

About two years ago, on my return from abroad, not without some skepticism, I decided to start a consecutive series of cases, reasoning that, the procedure being harmless, it would always be possible to perform one of the classic operations if the cyclodiathermy failed. During these two years I personally have done the operation in 68 cases, which I have divided into two series. The first comprised 53 eyes, in 46 private patients. These were all of chronic simple glaucoma (in 30 the glaucoma was considered to be the narrow-angle type and in the rest of the so-called open-angle type). In the second series were 15 eyes with what was considered secondary and complicated glaucoma. The latter group consisted of three aphakic eyes in which tension developed from 6 to 12 weeks postoperatively. Two were in cases of acute inflammatory congestive glaucoma; two were cases of rubeosis iridis glaucomatosa, and eight had been operated on unsuccessfully, by other methods. Seven of these eyes were admittedly already badly damaged. Unquestionably, the best results in our series were seen in the first group, the cases of chronic simple glaucoma. In several instances the patients were sent to the hospital for preliminary study, and tensions were taken every two hours around the clock in an attempt to find a base line. Many of these patients were under pilocarpine medication for long periods with diurnal pressures of 25 to 35 mm. (Schiøtz), but with slowly advancing field defects. These are the cases in which iridencleisis had been resorted to in the past—a procedure which, even when not attended by immediate complications, leaves the eye morphologically and physiologically altered, to say the least.

In the first group, of 53 eyes, I have had, up to now, only 2 cases in which a second treatment was required to lower the pressure. I have had 19 of these eyes under observation for one year or more after operation. In all tension has been stabilized, with no further loss of fields. In four cases before surgery the fields were contracted within 10 degrees of the fixation point. In none of these cases have there yet been complications of any sort. On the operating table there is an immediate rise in pressure, varying from 60 to 80 mm. following treatment. Within 30 minutes the tension starts to fall, to about 30 mm. In one hour the tension is usually below 14 mm. After the operation we do not close the eye, and the patient is ambulatory. Ordinarily we keep the patient in the hospital overnight. The following day the pressure usually reads from 10 to 14 mm. (Schiøtz), and on subsequent days it may rise to 18 to 20 mm. This is the usual course of events. Examination with the biomicroscope may reveal a slight iridic reaction, which usually subsides within two or three days. In a given case of chronic simple glaucoma in which the pressure, in spite of use of drops, hovers between 25 and 35 mm. (Schiøtz), I do only 8 punctures, 2 in each corner; above this level I do 3 in each quadrant, for a total of 12. In the second, smaller group, of 15 cases of

secondary glaucoma, we obtained good results in about 40% in spite of the fact that half of the eyes were already hopelessly damaged. I realize that one and a half years is a short time and my series is small, but the results seem to me to indicate a trend.

DR. ADOLPH POSNER: Dr. Castroviejo has presented an impressive series of cases, which would seem to dispel any doubt as to the safety and feasibility of cyclodiathermy. I am glad that Dr. Castroviejo was so modest as to state that he regards this series as a preliminary one, or at least the report as a preliminary report. I should like to amplify one point of which I am sure Dr. Castroviejo, as well as others, is aware, that is, that in narrow-angle glaucoma, even during the noncongestive, or the latent, phase iridectomy is a preferable procedure because it eliminates the cause of the glaucoma. As you all know, in narrow-angle glaucoma the normal channels of outflow are adequate, but the iris block prevents the aqueous from reaching these channels. Iridectomy prevents and relieves iris block.

Dr. Castroviejo mentioned the successful use of acetazoleamide (Diamox) in acute congestive narrow-angle glaucoma to lower the tension. It is indeed dramatic to see with what rapidity this drug reduces the tension to normal, often within two to three hours. For this reason, I think that we have an excellent means of relieving the acute attack, at least temporarily, after which we can cope with the glaucoma by whatever method we choose. I believe that acetazoleamide acts by shrinking the contents of the vitreous chamber. I have recently postulated the theory that the acute attack of narrow-angle glaucoma is caused by forward suction of the iris toward the region of the canal of Schlemm, where the pressure is only 10 mm. Hg, and hence lower than the intraocular pressure. If the pressure behind the iris is lowered sufficiently by acetazoleamide, the region of Schlemm's canal becomes the area of negative pressure, the iris is sucked backward, and the angle opens. In chronic simple glaucoma and such types of secondary glaucoma as glaucoma capsulare and essential iris atrophy, cyclodiathermy is an excellent means of reducing the tension, even if the operation has to be repeated.

There is, however, one important theoretical point to consider. Chronic simple glaucoma is associated with a progressively increasing obstruction to the outflow of aqueous. The objective of a filtering operation is to increase the outflow artificially and thus maintain a normal rate of aqueous circulation. Cyclodiathermy, on the other hand, is assumed to act by reducing the formation of aqueous. Any significant reduction in aqueous formation may be expected to lead to a decrease in the amount of aqueous flowing past the lens, and would thus deprive the lens of its normal nutritional requirements, as well as of its means for eliminating the end-products of metabolism. I have written to Dr. Everett Kinsey, and he, in a personal communication, expresses a similar opinion. It is possible that other structures of the eye, especially the macula, depend for their function partly on the volume of aqueous flow. The reason I mention the macula is that in chronic simple glaucoma we know that macular vision is the last to be lost, and it is in those cases in which we artificially lower the tension that we fear a reduction in macular or central vision.

We are indebted to Dr. Castroviejo for developing a precise technique of cyclodiathermy, as he has done in the past with other operative procedures. There is no question that cyclodiathermy is a valuable and a safe procedure when applied judiciously in selected cases, especially when filtering operations may be inadvisable. It should also be considered with patients of the older age groups, because in those cases the cataract formation does not present such a threat, and also in patients with aphakic eyes and certain secondary glaucomas. However, for the present, and until we know more about the delayed effects of the physiology of the eye, I join with Dr. Castroviejo in thinking that it might be unwise to reject the standard procedures, such as iridectomy and fistulizing operations.

Efficiency and the Ophthalmodiagnostic Process: The Charles H. May Memorial Lecture. MR. JOHN FOSTER (by invitation).

This paper will be published in full in a coming issue of the ARCHIVES.

Truman L. Boyes, M.D., *Chairman*

Charles A. Perera, M.D., *Secretary*

Regular Meeting, May 17, 1954, Combined with Section of Obstetrics and Gynecology

Ocular Diseases Occurring During Pregnancy. Dr. Ellen F. Regan (by invitation).

There are four ocular conditions related to pregnancy: pigmentation of the skin of the eyelids, retinopathy associated with hyperemesis gravidarum, retinopathy associated with toxemia of pregnancy, and asthenopia.

The use of corticotropin and cortisone in large doses for ocular disease in the early or late stage of pregnancy is to be avoided.

Idiopathic detachments of the retina occurring during pregnancy are to be treated promptly. A history of retinal detachment or its presence is not a contraindication to spontaneous delivery.

Meningiomas and other brain tumors may cause visual symptoms and field changes during pregnancy. These may disappear after delivery.

Retinal Findings in Pregnancy. Dr. Stuart S. Snyder (by invitation).

Examination of the ocular fundus is helpful in the management of patients with toxemia of pregnancy or with diabetes mellitus. Changes in the arterioles are divided into four grades.

Pregnancy in patients with severe preeclampsia and Grade 2 retinal arteriolar changes was terminated prematurely in 70% of the cases. The presence of Grade 2 changes with local or general arteriolar spasm suggests that the pregnancy be terminated within two or three weeks. Relaxation or disappearance of these changes before delivery in a severely toxemic patient means intrauterine fetal death.

Whenever Grade 3 or 4 retinal findings are noted, interruption of the pregnancy is indicated.

In hypertensive and renal disease associated with pregnancy, if retinal arteriolar changes are present during the first trimester, they were probably present before the start of the pregnancy. Women with malignant vascular hypertension should not become pregnant.

The presence of diabetes in pregnant women with toxemia increases the possibility of fetal death. Patients with diabetic retinopathy should not attempt pregnancy.

Value of Retinal and Conjunctival Vascular Findings in Normal and Toxemic Pregnancies. Dr. Robert Landesman.

1. In severe vomiting of pregnancy, retinal observations are indicated. Extensive multiple hemorrhages require interruption of pregnancy. Small hemorrhages may be watched during therapy.

2. In preeclampsia the presence of advancing spasm Grade I to II indicates an increase in the severity of the toxemia. In severe preeclampsia with Grade II changes, it is usually advisable to terminate the pregnancy prior to three weeks from the onset of the toxemia.

3. If the retinal changes remain the same or decrease, this is not an indication of improvement in the toxemic process. A sudden improvement may indicate fetal death.

4. In acute toxemia the vascular changes usually return to normal within three months. If postpartum changes persist, chronic vascular disease is probably present.

5. Retinal hemorrhage and transudate require immediate interruption usually within one week. In preeclampsia the fetal death rate with Grade III is 33%, and in hypertension it increases to 75%. This difference is related to the time of onset of the toxemia.

6. In eclampsia the presence of advanced retinal changes, Grade II or over, is usually associated with early onset of the toxemia, death of the fetus, and recurrent toxemia. Eclampsia at term, intrapartum or postpartum, usually is associated with minimal retinal changes.

7. Hydatidiform mole may give extensive localized and generalized retinal arteriolar spasm. Early onset of this process in the second trimester should suggest this diagnosis.

8. Ophthalmoscopy is most valuable in essential hypertension of the severe variety; Grades III to IV indicate immediate interruption.

9. In evaluating chronic hypertension and determining the chances of obtaining a live infant, careful retinal observations indicate the severity and duration of the hypertensive disease. The presence of silver-wire arteriolar reflexes and Grade II spasm early in or prior to pregnancy would suggest a poor prognosis for a living infant. If hemorrhages are evident, pregnancy is contraindicated, and therapeutic abortion should be performed.

10. The development of albuminuria and Grade II retinal change with a diastolic pressure of 110 mm. usually indicate almost no fetal growth. Fetal death in three weeks is to be anticipated. Termination of pregnancy should be planned, depending upon the duration of the pregnancy.

11. In chronic renal disease any change in the retinal vessels suggests a poor fetal prognosis. On the other hand, normal fundi would indicate a good fetal outcome.

12. Retinal arteriolar changes of any variety in the diabetic are a serious complication, particularly prior to pregnancy or in the first trimester.

13. The presence of diabetic retinopathy of any extent prior to or early in pregnancy offers a very poor fetal prognosis. With rare exceptions, living infants have not been obtained, and undersized infants are the result. Extension of the diabetic retinopathy is almost universal, and visual disturbances are common. Certainly, in the diabetic mother the ophthalmoscope ranks in importance with the stethoscope.

The conjunctival studies add further clinical evidence of the extent of vascular spasm in toxemia.

These observations of the conjunctiva are limited in our study to 200 patients with toxemia.

The conjunctival arteriolar spasm is especially prominent in the women with severe hypertension in the second trimester. The capillary ischemia is an indication of toxemic severity at term. The presence of extensive capillary tortuosity suggests underlying vascular disease.

DISCUSSION OF THREE PRECEDING PAPERS

DR. NELSON B. SACKETT: Dr. Regan has told us of various interesting eye conditions occurring in pregnant women. Could she tell us how many of these conditions were permanent, and, therefore, whether she would recommend that pregnancy be avoided or interrupted?

DR. LOCKE L. MACKENZIE: I notice that some patients who have not worn glasses previously are more comfortable with them during pregnancy, but may dispense with them afterward, or that those who do wear glasses frequently have to change them during pregnancy. I should like to ask for an explanation of this.

DR. BYRON SMITH: Biomicroscopic studies of the fundus have been done with the Zeiss slit lamp and Hruby lens. May I ask Dr. Snyder whether he has made any attempt to correlate the capillary status of the fundus with the conjunctival observations?

DR. STUART S. SNYDER: As far as I know, there has been no correlation.

DR. ELLEN F. REGAN: From my present point of view, the indications for interrupting pregnancy are, first, the presence of a brain tumor, and this is a diag-

nostic decision to be made by the neurosurgeon; and, second, the presence of eye changes in the mother or father which have a hereditary basis. Again, that is very far afield from what we have talked about.

So far as asthenopia goes, it means strain or eye fatigue.

The wearing of glasses in pregnancy is an individual problem. I am sure all have seen patients who have had a great deal of trouble during pregnancy and have worn glasses at that time. I do not know why they have their trouble. I have listed the reasons that have been suggested. My opinion is that if the patient has some latent refractive error or some latent muscle imbalance, anything that impairs the general health will make it manifest. There is also, of course, a large neurotic element, which comes into play at times.

Dr. Nelson B. Sackett: Clarification is needed on the status of the New York State law on interrupting pregnancy in the case of diseases which Dr. Regan has mentioned, and also in the case of virus diseases, such as rubella.

Dr. Abraham L. Kornzweig: Recently a problem came up at Mount Sinai Hospital, that of interrupting the pregnancy of a woman who had had a retinal detachment in one eye. She had loss of vision in that one eye, and the question came up whether she should be allowed to go through the pregnancy and perhaps endanger the vision of the other eye. The subject was looked up from the point of view of the State's legal requirements. The State requires that pregnancy can be interrupted only if the life of the mother is in danger; therefore, that lets us out almost completely, because most eye conditions do not in any way endanger the life of the mother.

Dr. David I. Mirow: I had under my care a patient with a blind eye as a result of absolute glaucoma and with chronic simple glaucoma in the other eye for a number of years. The eye had a very constricted tubular field, with vision of about 20/40 with glasses. She was pregnant and in fear of becoming totally blind and inadequate as a wife and mother to the family. She and her obstetrician urgently requested the interruption of pregnancy. On the basis of my findings and the gradual loss of the field and vision since her previous child, and the realization of the probable outcome of this case, I concurred in the decision to terminate the pregnancy and made a written recommendation to that effect. This was accepted by the respective authorities, and, as I understand, the procedure was carried out.

Dr. Nelson B. Sackett: Is the implication that the danger was to the woman's life or health?

Dr. David I. Mirow: There was no danger to life, but there was danger to her health in the progressive loss of central and peripheral vision.

Dr. Locke L. Mackenzie: The law states that therapeutic abortions can be performed in any situation which endangers the life of the mother or baby. That seems a ridiculous statement, because the abortion will destroy the life of the baby; but it brings up the question of whether or not there might be a legal cause for therapeutic abortion in women who had had rubella. I should like to hear what the ophthalmologists feel about the incidence of eye lesions in the baby following this disease in the mother.

Dr. Charles A. Perera: Abortions have been performed in the presence of rubella in the first two or three months of pregnancy because of the observations in the literature, which indicate a high proportion of abnormal children born as the result of this condition. Reese has raised the question regarding children of patients who had had one eye removed for retinoblastoma and survived with one normal eye. Reese has demonstrated from statistics that a very high percentage of the children of such a parent have retinoblastoma also. This brings up the question of whether it is better not to have children than to require abortion. All we can do is to advise patients what we should do if this situation were in our own family. I should be very loath to let my wife go through with a pregnancy if she had rubella in the first two or three months. I am quite sure the obstetrician will consent to the termination of pregnancy in severe toxemia, though there may not be a legal basis for it.

DR. NELSON B. SACKETT: That applies to acute glaucoma, too?

DR. CHARLES A. PERERA: I do not agree; I think in Dr. Mirow's case it may have been wise to do the abortion. We have all seen glaucoma progress and advance, but I do not think there is good evidence that glaucoma is influenced by pregnancy in itself.

DR. FRANK SPIELMAN: Years ago the question of terminating pregnancy in rubella came up in relation to one of the pediatricians, who was repeatedly being called in to pass on the question of whether to do an abortion on that basis. He had so many consultations in regard to this question that he finally called the District Attorney, who laid down the positive rule that only in conditions which endangered the life of the mother could therapeutic abortions be performed; and since that time I believe the number of abortions being done for rubella has declined considerably. I should like to ask about two other conditions which may produce lesions similar to those associated with rubella. I do not think much stress is placed on the first, that is, mumps. The second condition which has been an indication for abortion in the past is retinitis pigmentosa. I should like to ask Dr. Regan whether, in her consideration of the eye conditions which may occur during pregnancy, she has come across any reference to the question of hormones as they affect eye conditions. One of the things which is very much debated at present is the use of various hormones during pregnancy—in relation to toxemia as well as to diabetes. I should also like to ask whether detachment of the retina can occur as a result of the thrashing about during actual labor of a patient who is very nervous and excitable.

DR. ELLEN F. REGAN: In answer to the question about the effect of hormones on eye conditions during pregnancy: The excretion of corticosteroids is increased during the first and third trimester. It is less in the second trimester and after delivery. This decrease has therefore been postulated as an indication for cortisone or corticotropin therapy for optic neuritis in the postpartum period. It must be emphasized that this problem has not been studied extensively.

I have no specific evidence to explain why detachment of the retina occurs during delivery.

I have no specific information about retinitis pigmentosa.

DR. STUART S. SNYDER: We found that medical treatment with hormones has been unsuccessful in cases of hypertension and diabetes, especially rutin and testosterone; but we feel we can help some of these patients by watching the retinal arterioles.

DR. ROBERT LANDESMAN: If one were to select one condition in which the ophthalmologist would be of the greatest value to the obstetrician, it would probably be diabetes; and I believe that the diabetic should be followed carefully in pregnancy, both by the obstetrician and by the ophthalmologist.

The legal indication for the interruption of pregnancy in toxemia is primarily concerned with the fetus, which will die in utero if not delivered. In conclusion, the retinal picture in toxemia is one other clinical observation that the obstetrician may use to evaluate this unknown disease entity.

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Edmund B. Spaeth, M.D., *Chairman*

William E. Krewson, III, M.D., *Clerk*

March 18, 1954

Krönlein Orbitotomy for Neuroma of Optic Nerve (A Motion Picture). DR. EDMUND B. SPAETH.

In the consideration of the surgical therapy of orbital neoplasms the surgeon must frequently make a difficult decision. In the case under consideration, should an external orbitotomy be performed by the ophthalmologist, or should a transfrontal craniotomy be done by a neurosurgeon and the orbit entered via the roof of the orbit in the frontal cranial fossa—a so-called uncapping of the orbit?

This consideration was not a part of the moving picture demonstration. The moving picture presented was shown to illustrate the easily carried out surgical procedure for an optic nerve neoplasm through an orbitotomy. It is quite proper to say that a transfrontal craniotomy for this condition is wholly unnecessary. It is true that while a transfrontal uncapping of the orbit is practically free of mortality, it is much more frequently complicated by subtotal to complete oculomotor paralyses, including ptosis. A far greater incidence of this complication occurs with the craniotomy.

Recently, in carrying out the technique of a Krönlein orbitotomy, surgeons have been using an oscillating saw for the bone wedge resection. While there is no difficulty with this saw, the essayist emphasized that a simple brace and bit and Gigli saw are equally satisfactory, with no increase in tissue trauma, and these, for the occasional operator, are much less expensive.

A T-shaped incision is made, the "T" lying upon its side with the cross line curved to parallel the rim of the orbit. The periorbita is loosened from the bone at the rim of the orbit and detached with a blunt periosteal elevator well into the depths of the orbit on the lateral wall. It is a simple matter to carry this blunt dissection down to the lateral lip of the superior and inferior orbital fissures. With a brace and bit (a hand-driven one is adequate), the lateral orbital wall is perforated at the base of the lateral angular process and at the base of the zygomatic process, where it takes off from the zygoma itself. The rim of the orbit is cut through with a Gigli saw threaded through these perforations, and the bone wedge resection is completed with a mallet and chisel. The orbit is then entered through a lateral horizontal incision in the periorbita, the lateral rectus muscle identified, and the intraorbital surgery necessary carried out with full and adequate visibility.

In the instance shown in the moving picture the tumor of the optic nerve was exposed, and a neurectomy performed within the muscle cone, without damage to any of the muscles. The eyeball was then strongly rotated into adduction so that the optic nerve and its neuroma were in full view, making a resection of the nerve from the globe a very simple procedure.

The incision is closed in the periorbita after careful hemostasis; the wedge of bone is elevated to its normal position and sutured in place with 000 chromic absorbable surgical (catgut) sutures through the periosteal edges, fascia, orbicularis fibers, and lateral raphe of the orbicularis; the tissues are closed with absorbable surgical sutures, and the skin is closed with black nonabsorbable surgical (silk) sutures. The case is dressed with the same type of pressure dressing one would use for a fractured orbit.

Experiences with Acetazoleamide (Carbonic Anhydrase Inhibitor; Diamox) in Glaucoma. Dr. Irving H. Leopold, Dr. I. J. Eisenberg, and Dr. Jules Yasuna.

Carbonic anhydrase is an enzyme which interacts with bicarbonate to liberate carbon dioxide and water. This enzyme can facilitate the reaction in the reverse direction. There is evidence that the enzyme carbonic anhydrase exists in ocular tissues, such as the lens (Bakker); iris, choroid and retina (Leiner, 1943), and ciliary body (Wistrandt, 1951). Acetazoleamide is a carbonic anhydrase inhibitor that has received considerable use as a diuretic. At present it is under wide-scale investigation for its possible ability to lower intraocular pressure (Becker, Thorpe, 1954).

This agent has been tried at the Wills Hospital in 51 paients, representing 90 eyes with a variety of types of glaucoma, in all of which the pressure had previously been uncontrolled by miotics and/or surgery prior to the use of acetazoleamide. In this series, acetazoleamide, in doses ranging from 125 to 1,000 mg. per day, lowered intraocular pressure in eyes with narrow-angle glaucoma, wide-angle glaucoma, glaucoma secondary to cataract extraction, glaucoma secondary to uveitis, pigmentary glaucoma, glaucoma capsulare, and infantile glaucoma. It had its smallest degree of success in glaucoma secondary to venous occlusion and

glaucoma associated with rubeosis iridis diabetica. It was initially successful in less than 50% of the cases of glaucoma associated with traumatic hyphema. The onset of action following the oral instillation of the drug could be noted as early as 30 minutes. The duration of effect varied in individual eyes from 2 to 12 hours following a single dose. Not all eyes which were benefited initially continued to benefit over a three-month period of observation. Some were no longer effectively controlled by acetazoleamide plus miotic therapy. However, there were 16 eyes in this series with varieties of chronic glaucoma, previously uncontrolled by various surgical procedures and miotics, which have now been controlled by miotics plus acetazoleamide for over three months.

Acetazoleamide has some undesirable side-reactions. Approximately 75% of the patients noted paresthesias of the hands, feet, and/or face. Approximately 25% were drowsy. One patient was disoriented, and 10% of the patients had gastrointestinal symptoms, including anorexia, nausea, and vomiting, and occasionally diarrhea. Ten of the patients refused to continue the drug because of these side-reactions. No case of agranulocytosis or skin reaction was noted.

The mechanism of the ocular action of this drug is not known. Other diuretics, such as mercaptomerin (Thiomerin), a mercurial diuretic, will produce a fall in intraocular pressure. This was noted in 10 normal patients. The time of onset of the pressure-lowering effect was much longer after the administration of mercaptomerin than after acetazoleamide.

Tonographic studies done on most of these patients have demonstrated no change in the coefficient of aqueous outflow after the administration of acetazoleamide, suggesting that there is a decrease in the formation of intraocular fluids. Paracentesis done on experimental animals revealed that prior administration of acetazoleamide increased the time required for the restoration of the intraocular pressure and for re-formation of the anterior chamber as compared with eyes in animals without acetazoleamide. This is additional evidence that acetazoleamide interfered with formation of intraocular fluids. In six patients it was noted that positive water provocative tests could be rendered negative by the ingestion of acetazoleamide.

The administration of 2 to 3 gm. of sodium chloride or 2 gm. of sodium chloride and 1 gm. of potassium chloride to patients on acetazoleamide therapy ameliorates most of the side-reactions, such as drowsiness, numbness, and tingling. However, the intraocular pressure previously controlled by miotics and acetazoleamide was no longer controlled when the sodium chloride or potassium chloride was added to the therapy.

Because carbonic anhydrase may be playing a role in the active transfer of bicarbonate ions across the blood-aqueous barrier and into the aqueous humor, it was thought advisable to measure the bicarbonate levels in the eye and blood of rabbits before and after the administration of acetazoleamide. These measurements were determined at intervals of 1, 3, 6, and 15 hours after injection of acetazoleamide intravenously (Green, Capper, Bocher). The values obtained revealed that the bicarbonate of the blood plasma fell below normal levels in one to six hours, whereas the aqueous humor levels of bicarbonate were normal at one hour but fell at the sixth-hour determination. Both the blood plasma and the aqueous humor returned to normal levels by 15 hours. The relative drop in blood bicarbonate was much greater than that in the aqueous. Not all the rabbits showed a drop in intraocular pressure.

This question was approached in another manner, in which the carbonic anhydrase activity of the ciliary-iris tissue was determined before and after acetazoleamide administration in a Warburg apparatus, and the data demonstrated a marked inhibition of carbonic anhydrase activity of the ciliary and iris tissue within one hour after the intravenous administration of acetazoleamide.

Although these data indirectly suggest some influence on carbonic anhydrase activity in the eye, there are other possible mechanisms by which this drug can be acting. It may be altering the pH of the ocular tissues, e. g., ciliary body or vitreous. The drug may be producing a secondary effect, such as the stimulation of some

hormonal substance from one of the endocrine glands, such as the pituitary. It is known that diuresis may stimulate the formation of pituitary antidiuretic hormone. This hormone theoretically would tend to elevate intraocular pressure, but other mobilized hormonal substances might have a tension-lowering effect. No evidence could be found in these patients for any alteration in scleral rigidity that could be attributed to acetazoleamide therapy.

DISCUSSION

DR. HAROLD G. SCHEIE: Each generation of physicians regards its own age in medicine as the golden one. I believe, however, that my own has been particularly favored. When I was an intern, sulfonamides were first introduced. Since that time, chemotherapy has achieved its present status, and antibiotic therapy has been even more miraculous. Hormonal therapy has been equally astonishing. Now, apparently, we are witnessing still another startling advance in the clinical application of our knowledge of the physiology of respiratory enzymes.

When I was a resident, assisting with some of Dr. Adler's studies on aqueous physiology, theories as to the mechanism of the formation of aqueous were much more nebulous than they are today. Duke-Elder favored the theory of dialysis, but, in this country, Adler, Friedenwald, Kinsey, and others were not convinced that secretion, at least, was not an important factor in its production. Friedenwald developed his reasoning to the point where he suggested that secretion of aqueous by the ciliary body was linked to certain respiratory enzymes. The effect upon ocular tension, which results from the effect of acetazoleamide in inhibiting carbonic anhydrase, seems to support such reasoning.

As Dr. Leopold has said, there is as yet no final proof as to how acetazoleamide (carbonic anhydrase inhibitor) exerts its effect, but it certainly seems to diminish aqueous production. My colleagues and I are carrying out investigations along somewhat the same lines as the present authors. Our observations seem to bear this out, as did Becker's. Our clinical results are quite parallel to Dr. Leopold's, although recorded on a smaller number of patients, observed for a relatively short period of time; however, I believe our results are even more uniformly good. We have noted almost invariable reduction in ocular tension to normal except in absolute glaucoma.

However, some reservations must be maintained. I have talked, in the last two days, to Dr. DeVoe and his group in New York City. They have found that patients with simple glaucoma usually develop a resistance to acetazoleamide after two or three months and the tension rises once more. They believe that the usefulness of the drug will be chiefly that of an adjunct to tide the patient over acute phases of glaucoma. This would seem of importance in acute congestive glaucoma and in certain secondary glaucomas, for example, that associated with traumatic hyphema, in which we have noted excellent results. They have also encountered cutaneous reactions to acetazoleamide, as might be expected with sulfonamide therapy. We have had two patients with renal symptoms of calculi. This may have been coincidental, or it is possible that calculi, present beforehand in the renal calices, became fragmented when the pH changed from acid to alkaline, and became dislodged, to cause ureteral symptoms.

A thought that gives me pause is that we may be substituting one abnormal state for another by markedly diminishing production of aqueous. All know, for example, that cataract can develop when aqueous formation is reduced and nutrition of the lens is poor, as in the phthisical eye. Until more information is available, it seems advisable to employ acetazoleamide with some caution, probably when conventional methods have failed.

DR. I. S. TASSMAN: Would it be advisable at the present stage to use acetazoleamide with patients in routine office practice outside the hospital?

DR. IRVING H. LEOPOLD: It is possible that this drug may have other toxic features. Dr. Scheie mentioned allergic skin reactions, and the possibility of interference with normal ocular tissue metabolism by virtue of reduced ocular fluid formation.

The lens has been shown by Barker to contain a great deal of carbonic anhydrase. Perhaps acetazoleamide will be able to penetrate through the lens capsule to inhibit the carbonic anhydrase in the lens. If so, it might interfere with its metabolism directly.

I can see no objection, Dr. Tassman, to the ophthalmologist's using acetazoleamide in his office if he is familiar with the side-effects and contraindications of the drug. One should be familiar with the renal status of the patient before applying any diuretic agent, have information about the patient's salt intake prior to the administration of the drug, and recognize the possibility of the patient's idiosyncrasies and hypersensitivity. Many cardiac patents have been carried on this drug for a year and a half to two years without untoward results.

Radioactive Phosphorus in the Diagnosis of Intraocular Tumors. DR. JOHN ERBAUGH.

While it is readily apparent that lesions of the anterior part of the eye can be detected in vivo, we do not feel that anything conclusive can be stated about posterior lesions. The problems involved in detection of a lesion farther from the counter than the maximal range of beta radiation are not as yet solved. Further, the ciliary body interposes a radioactive screen that further reduces the sensitivity of the test. Although in our 20 cases of detachment the phosphorus studies have agreed with the clinical diagnosis, it is probable that the large size of the lesions was responsible for their detection by a radiosensitive counter.

DISCUSSION

DR. J. EISENBERG: Since Thomas first recorded the use of radioactive phosphorus in the detection of intraocular tumors, we at the Wills Hospital have performed a P^{32} concentration test on approximately 200 patients. From the observations that were made on these patients we came to certain conclusions.

1. There is no normal range for P^{32} concentration.

2. If the normal point of reference can be established, an intraocular neoplasm can be detected. This we have done.

Bettman recently reported that certain areas of the globe show a significant variation of P^{32} concentration, especially if the counter is placed over the external rectus muscle. We, too, have found this to be an obstacle. This difficulty was overcome by establishing our reference point at the limbus and avoiding any count over the medial rectus muscle near the canthus in the pathologic eye. The other external muscles do not appear to affect our criteria for a positive concentration P^{32}.

3. If the concentration of P^{32} in the lesion is increased 30% or more than the average in the normal reference point, the test should be considered positive.

In using this percentage, we encountered one major difficulty. An inflammatory lesion, especially if active, also gives an uptake of over 30%. This leaves the problem of trying to differentiate between inflammatory and neoplastic lesions.

On the basis of some of the work done by Jones in 1940, and reported in the *American Journal of Cancer*, it was felt that neoplastic tissue would retain phosphorus for a longer period of time than corresponding normal, or even inflammatory, tissues. Working on this hypothesis, we ran a time curve, and, much to our gratification, we were able to show that tumors in the eye will show in one hour an increase of 30% or more as compared with the average in the normal eye, and that in 24 hours this increase will be even greater. In inflammatory lesions there was a fall in the 24-hour uptake. This enabled us to differentiate malignant from inflammatory lesions in the area accessible to our counter. At the present time this is not reliable for lesions in the posterior segment.

Even though we feel that this test has great value, its usefulness has still certain limitations. It should not be used (1) with a one-eyed patient, (2) when both eyes are pathologic, or (3) in making counts over the medial rectus muscle near the inner canthus.

DR. HOWARD BEDROSSIAN: I should like to mention a few points that are frequently omitted in discussing the technical difficulties encountered in performing this test. At the Graduate Hospital we have had 30 cases, of which 2 showed a positive uptake. The remaining cases all showed negative results. Two of our negative results were in patients who had posterior lesions. Although the P^{32} studies were negative, clinically the patients were thought to have a tumor; so the eye was removed. The Geiger counter was then placed directly over the tumor and the previous negative results then became positive, showing the technical difficulty in getting the counter back far enough in the case of posterior lesions. Our two positive results were in patients with anterior lesions.

Another problem which arises in evaluating the percentage uptake is in making certain that the readings are not in error. For example, in some patients after the injection of P^{32} we obtain about 400 counts per minute, whereas in other patients we sometimes get as much as 800 counts per minute. One can easily see that a difference of 50 counts would be a greater source of error in the first patient, with 400 counts per minute, than it would in the second patient, with 800 counts per minute. For this reason, the person who is performing a P^{32} study must have a great deal of patience and be willing to repeat the readings over the different quadrants if there is any question about the reliability and consistency of the readings. Theoretically, it should take about four minutes to examine each eye, but there have been many times when I have spent one hour with the patient, repeating the readings until I was satisfied that they were accurate.

As Dr. Eisenberg has mentioned, we, too, have noted a slight increase in the number of counts when taken over the medial rectus muscle. In addition, we have noted also the tendency toward increased counts when the readings are taken over the inferior rectus muscle. This may be due to the increased amount of conjunctival tissue in the lower cul-de-sac which comes up around the Geiger counter. Normally there is not as much conjunctival tissue around the Geiger counter when it is placed in the region of the superior or the lateral rectus muscle.

It is my feeling that this test will be more reliable if it is performed by the same operator, who would be constantly aware of the possible sources of error.

Perce DeLong, M.D., *Chairman pro tem*

William E. Krewson III, M.D., *Clerk*

April 15, 1954

Congenital Corneal and Facial Anesthesia: Report of a Case. WILLIAM C. FRAYER, M.D. (by invitation).

Corneal and facial anesthesia as a result of congenital defects in the fifth cranial nerve has been infrequently reported. Because definite proof of nuclear or nerve aplasia has been lacking in these reports, some authors have denied the existence of such an entity. A child with bilateral anesthesia of the cornea and of the skin of the face in the distribution of the fifth nerve, noted shortly after birth, has been observed for the past four and a half years at the Children's Hospital of Philadelphia.

The patient was first admitted to the Children's Hospital on Sept. 7, 1949, at the age of 5 months. He had been born with imperforate anus and a rectovesical fistula. Operative repair of these anomalies on the day of birth had resulted in a rectal stricture, and the child was referred to the Children's Hospital for evaluation. Routine ocular examination at this time was negative, although corneal sensitivity was not tested. After repeated rectal dilations, the patient was discharged from the hospital but was readmitted on Nov. 3, 1949, because of bilateral corneal ulcer and malnutrition. Examination confirmed the presence of ulceration of both corneas in the exposed areas, with very little ciliary or conjunctival injection. Neurological examination revealed loss of sensation to pinprick over the face and forehead in the distribution of the fifth cranial nerve bilaterally. Skull and chest x-rays were negative. Laboratory examination of the blood and urine, serological tests for syphilis, and the tuberculin test were all negative.

The corneal ulcers could not be controlled by local and systemic use of antibiotics or by careful shielding of the eyes. Prompt corneal healing occurred, however, after bilateral median tarsorrhaphy was performed. The lids were reopened after the child had been symptom-free for one year, but lateral tarsorrhaphies were performed in August, 1952, because of subsequent breakdown of the corneal epithelium.

During the period of observation it became increasingly evident that the child's mental and physical development were markedly retarded. At the age of 5 years he was still unable to sit or stand alone. He showed marked general muscular atrophy, hyperreflexia, and a limited awareness of his environment. A large ulceration of the skin of the forehead developed as a result of rubbing the head against the floor and other rough surfaces.

Feeding was a constant problem. On March 3, 1954, the patient refused food altogether, and he was admitted to Children's Hospital on March 11, 1954, with marasmus, dehydration, septicemia, and multiple skin abscesses. Supportive measures failed and he died on March 14. It is unfortunate that permission for necropsy could not be obtained.

Although true congenital aplasias of the third, sixth, and seventh cranial nerve nuclei are said to occur occasionally, absence of the fifth nerve nucleus has never been proved. Ford has stated that, as far as he can determine, sensory defects of the fifth nerve do not occur congenitally. Cases of corneal anesthesia, thought to be on a congenital basis, have been reported, however, by Lawford and Kayser. Francheschetti reported the four-generation pedigree of a family with diminished corneal sensation associated with herpetic lesions of the cornea. Acquired causes of nerve damage, such as wounds, fractures, meningeal infections (notably syphilis and tuberculosis), tumors, hemorrhage, and aneurysm, must always be ruled out; but Kinnier Wilson stated that the presence of other congenital anomalies, or a hereditary occurrence of hypesthesia, must be considered evidence in favor of nuclear aplasia.

The case reported here is presented as a possible example of true congenital corneal and facial anesthesia. The coexistence of other congenital anomalies and the failure to uncover evidence of acquired causes of nerve damage are factors which tend to support this contention.

DISCUSSION

Dr. George D. Gammon: Dr. Frayer has given a succinct presentation of this case, illustrating some of the difficulties in coming to a conclusion concerning the origin of the patient's defect. I saw this child only once, at the age of 5 months, and, unfortunately, did not see him in his later years. He was seen in the neurological clinic at the Children's Hospital, however, at the age of 5 years, at which time attention was not focused on whether he had a congenital absence of fifth nerve function; rather, because the child has been at the mental institution and had deteriorated while there, the problem of his disposition was the one that was of most concern at the moment. It was apparent, however, to the physician who saw him at the clinic that the child was very backward in many other functions and in sensation. He was unable to stand without support, but when he was held up, he could make stepping movements. It is said that he was scarcely aware of his environment, but that occasionally he would respond to a sound with a smile. He seemed not to respond much to tactile or pinprick sensation. As I said, unfortunately this examination was not a detailed one, with the purpose of determining whether this defect represented a congenital anomaly of the sensory region of the fifth nerve. From the point of view of classification, it may be said that this child, who had several congenital defects, aneurysms among them, and I believe a fistula, had also failed to develop. He was spastic, with a bilateral Babinski sign, and was completely devoid of speech or obvious sensation at the age of 5 years. I am stating this on the basis of notes rather than on personal observation. He apparently had the corneal anesthesia at 5 months of age, accompanied by the ulceration described. It might be helpful to consider the possibilities of such a condition in the abstract and see whether any of them can be applied in this case.

As Dr. Frayer has said, congenital absence of function of cranial nerves has been mostly of the third, sixth, and seventh nerves. The exceptions are the special senses of vision, hearing, and taste, of which cases of congenital absence have been reported. There are occasional reports in which either acquired decompression or compression of nerve by congenital anomaly has occurred. I recall a chap who had a peculiar distribution of bone anomaly at the base of his skull, with a fifth and seventh nerve involvement; the latter proved transitory, curiously enough, although there was the large hump on the base of the middle fossa. In the recognition of pain sense, one must have a peripheral apparatus, by which impulses concerned with pain are conducted inward to reach the muscle, and ultimately the cortex. Of course, an interruption of any of these pathways as it travels within the peripheral or the central nervous system can result in the failure to recognize pain in the territory of that nerve. In recent years, however, from the work of frontal lobotomy, it is apparent that the reaction to pain differs, or the appreciation of pain may differ through the lesion in the frontal lobotomy, and, although the patient is able to perceive pain, he does not react to his pain and does not complain of it. There is another specific mechanism in which unawareness of pain or failure to react to pain can occur, that is, with lesions in the supermarginal gyrus, in which a disturbance of the body scheme occurs. It is the sort of thing in which the patient is unaware of the opposite side of his body, or may be unaware of paralysis on the opposite side of his body. This has been reported in a few instances in which pain, as well as failure to recognize pain, was a part of the picture, and when the lesion has been cleared up the disturbance has proved to be transitory.

Finally, there is the situation in which there is apparently a congenital inability to feel or to react to pain. This is universal in the sense that the whole body is involved. A few cases of that sort have been described, some recognized in childhood; and the patients have had pain, fractures, perforated viscera, etc. As far as I am aware, there are no pathological data in those cases as to the location of the lesions, if any, which are responsible for the failure to recognize pain as a painful sensation. Where the present patient would fit into these various possible categories I do not know. Dr. Frayer has said that I have made a, I am sorry to say rather superficial, search in the neurological literature, and I have not found any description of congenital absence of the fifth nerve function alone.

Retinopathy in 500 Unselected Diabetics. Dr. T. H. Cowan and (by invitation) Dr. P. L. Carmichael and Dr. F. Campagna.

The fundi of 500 unselected diabetics were examined by the authors to determine the incidence of diabetic retinopathy in the diabetic population and the relationship of the degree of retinopathy to the control, severity, and duration of the disease.

The basic lesions of diabetic retinopathy were considered to be small round hemorrhages and small sharply defined, hard, yellow-white exudates. For the purpose of study, the patients with retinopathy were grouped into four categories, ranging from involvement with few hemorrhages and exudates to the typical proliferative retinopathy. Any additional fundus lesions which were not considered to be a part of the true diabetic retinopathy were listed under separate headings.

Venous aneurysmal dilatations were subjected to special study, since at present they are considered to be one of the earliest signs of diabetic retinopathy. They were present in only 37 (7.4%) of the 500 cases in this series. Of these 37 cases, only 9 were found in otherwise normal fundi.

Arteriosclerosis was found to be present in only 100 cases (20%).

Some degree of diabetic retinopathy was present in 216 (43.2%) of the cases. Of the total diabetic population, only 34 cases (6.8%) fell into Categories III and IV (severe and very severe retinopathy).

The standard criteria of diabetic control were used to place the patients into three groups, of good, fair, and poor control. It was found that there was little correlation between the control of the diabetic patient and the incidence and severity of the retinopathy.

Similarly, the severity of the clinical diabetes seemed to have very little influence on the degree of retinal involvement. Severity, in contradistinction to control, includes the incidence and degree of diabetic complications, such as gangrene, peripheral vascular disease, and arteriosclerotic heart disease.

With the passage of time there is a definite increase in the incidence of diabetic retinopathy of all types. Of 228 cases in which the duration of diabetes was five years or less, retinopathy was present in 64 (28%). Of 107 cases in which diabetes was present for 5 to 10 years, retinopathy was present in 48 (45%). In those cases in which diabetes had been present for 10 years or longer, the incidence of retinopathy rose to 61.5% and remained at approximately this level regardless of the duration of the disease (this study included patients who had diabetes for more than 30 years).

DISCUSSION

DR. STANLEY SPOONT: There is no doubt that Dr. Cowan has raised problems that are important to the internist. Degenerative vascular disease is a tremendous problem, especially in those patients who are kept alive long enough to develop such complications. It is extremely difficult to define the control of the diabetic patient. The internist sees these patients perhaps once a month and is necessarily unaware of the patient's status during the intervening period. The essence of the problem is the control of diabetes for years and years, and it is often impossible to perform the great number of tests that would be necessary to insure perfect diabetic control. However, a start must be made at some point, and I think Dr. Cowan has illustrated the standards that are usually used. It is also hard to define the severity of diabetes. Although there are no definite criteria, most people take an amount of insulin depending on the state of nutrition and the occurrence of acidosis.

It is interesting that we studied a similar series a few years ago at the University Hospital, in conjunction with Dr. Dyer and Dr. Day, and found the incidence of diabetic retinopathy about 42%. Dr. Cowan mentioned a 43% incidence, and Dr. Brill's group is again in the 40% range. Thus, I believe the incidence is close to this figure.

Dr. Dyer and I believe that the control of the diabetes is important. Others, including Tolstoi, in New York, take another view, and which one is correct will be decided in the future.

The factor which we consider the most important at present is the duration of the diabetes. I agree with Dr. Cowan that there are diabetics whose disease is so poorly controlled that they present blood sugar levels of 400 or 500 mg. week after week, and yet examination of the eyes fails to reveal any retinopathy. Surely, there must be conditions other than the control of the diabetes of importance in these patients. Some of these patients, youngsters generally, are on the verge of acidosis all the time, may be poorly nourished for years, and do not develop changes in the eyes.

Some interesting suggestions have been made lately regarding diabetic retinopathy. Perhaps the mucopolysaccharides of the blood are implicated, or the blood protein may be abnormal. Elevated blood fat levels in conjunction with renal lesions, often, if not invariably, associated with the retinal lesion, have an effect which at present is not very clear. Reports have appeared on the production of microaneurysms in patients' eyes following administration of corticotropin. Retinopathy in diabetics is some times made worse by pregnancy. All these observations suggest a hormonal effect of some sort. Some cases suggest that if, as Dr. Cowan suggests, a new picture of some endocrine imbalance is occurring in some of these cases, the adrenal gland may be implicated, although any certainty would be premature.

Clinical Evidence of Third Nerve Nuclear Arrangement. CAPTAIN FREDERICK HARBERT (MC), U. S. N. (by invitation).

The literature on third-nerve nuclear arrangement was reviewed, and four cases of unilateral upward gaze paralysis with and without ptosis were reported. The association of ipsilateral inferior rectus involvement of slighter degree was

reported, apparently for the first time. This may account for the large binocular field in many such cases, without changes in the position of the head being required. The classic bilateral functional arrangement postulated by Brouwer and Bernheimer is not supported by these clinical cases. The clinical evidence is consistent with the more recent experimental evidence of ipsilateral innervation by Szentágothai, Davis, Bender, and Weinstein.

DISCUSSION

DR. FRANCIS H. ADLER: Dr. Harbert has presented four cases in which definite paralysis of a superior rectus and an inferior oblique muscle was associated with paralysis of an inferior rectus muscle in the same eye. Since the other muscles in this eye supplied by the third nerve escaped, that is, the medial rectus and the internal ocular muscles, he places the lesion in the third nerve nucleus on that side. A nuclear lesion which would catch these three muscles can be better explained on the basis of the arrangement of the nuclei which has recently been found in animals by the use of the Horsley-Clark stereotactic apparatus than on the basis of the older arrangement proposed by Bernheimer and Brouwer. As Dr. Harbert states, cases of unilateral superior rectus and inferior oblique paralysis alone are not very rare. An associated paralysis of the inferior rectus on the same side is a very rare occurrence. (Slides of two cases illustrative of the former condition) The confusing part of the picture in these cases is that there is usually present an inhibitional palsy of the yoke muscle antagonists, suggesting a true paralysis of the inferior rectus and the superior oblique muscle of the opposite eye. It is difficult, and sometimes impossible, to determine which group of muscles is really paralytic and which muscles are merely obeying Hering's law and underacting on physiological principles. Most of these cases show either true ptosis or pseudoptosis, as reported by Kirby, but lid retraction may be present (illustrative slides of one case).

In my experience, it is extremely rare to find an inferior rectus palsy on the same side as part of this picture. Of the four cases reported this evening, Case 4 seems to meet best all of the criteria necessary to establish this diagnosis. The pictures show a strabismus in the characteristic motor fields of all three muscles, and the diplopia fields are in accord with these. The pictures of Case 1 show a definite left superior rectus and inferior oblique palsy. Further, on gaze down and to the right, a right hypertropia is evident. The measurements given show no measurable separation with gaze down and to the left. I find it hard to accept a paralysis of the left inferior rectus on the evidence given, but, knowing Dr. Harbert's extreme care in making such examinations, I am willing to accept it on faith. The right hypertropia on gaze down and to the right can be explained on the basis of inhibitional palsy of the right inferior rectus issuing from a left inferior oblique palsy, but it could also be said to be due to a true palsy of the right inferior rectus. This explanation would be in keeping with the Bernheimer arrangement of the third nerve nuclei, in which the inferior rectus innervation is supposed to be crossed to the opposite side of the nucleus. In Case 2 the pictures fit a paralysis of all three muscles, but the measurements were not entirely satisfactory. In Case 3 the pictures show a paralysis of the left superior rectus and the left inferior oblique, but the eyes look in alignment, or even suggest a right hypertropia on gaze down and to the left. Measurements showed 2 D. of right hypertropia on gaze down and to the right and 2 D. of left hypertropia on gaze down and to the left.

Until more of these cases can be collected and studied, as Dr. Harbert has done, it would seem wise to admit that our knowledge of the arrangement of the nuclei in the third nerve mass in man is still entirely conjectural. The evidence he has presented is valuable and points in the direction he has suggested.

DR. I. J. ISENBERG: Dr. Harbert placed the lesion in the nuclei. I should like to speculate on the possibility of a retro-orbital lesion causing the paresis of elevation. Would you mind commenting on that, please?

CAPT. FREDERICK HARBERT (MC), U. S. N.: In answer to Dr. Eisenberg's question about a retro-orbital lesion, I presume he was thinking of something between the sphenoidal fissure and the brain stem?

DR. I. J. EISENBERG: No, in the orbit itself—a space-taking lesion.

CAPT. FREDERICK HARBERT (MC), U. S. N.: In the first place, the third nerve divides at the superior orbital fissure, or perhaps just before it enters the orbit. The superior branch carries levator and superior rectus fibers, while the inferior oblique fibers go with the inferior branch. In the cases reported there is a mechanical involvement of superior and inferior muscles, which are innervated by different branches of the nerve. On that basis, we can rule out a single lesion that could account for this. We also have the medial rectus muscle completely spared in all these cases, again ruling out an orbital lesion. It would take a peculiar lesion to spare the medial rectus and give maximal involvement of the other two muscles that are innervated by the inferior division.

Dr. Adler's criticism is very proper. Perhaps I was a little too enthusiastic in reading inferior rectus involvement into some of the cases. However, I shall try to find better data to substantiate it, and if I can, I shall present them to you.

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Basic Course in Orthoptics for Technicians.—The Basic Course in Orthoptics for Technicians, sponsored by the American Orthoptic Council, will be held this coming year in the Department of Ophthalmology, University Hospitals, Iowa City, from June 20 through Aug. 13, 1955. As usual, there will be didactic lectures and practical demonstrations, given by an outstanding faculty.

Further information, as well as application blanks, can be obtained by writing to Dr. Hermann M. Burian, Department of Ophthalmology, University Hospitals, Iowa City.

XVI All-India Ophthalmological Conference.—The XVI All-India Ophthalmological Conference will be held in Bombay in the first week of March, 1955. The conference is devoting its scientific session to a symposium on Diseases of the Lacrimal Apparatus. It also plans to hold scientific and trade exhibitions of ophthalmic interest. Further information can be obtained from the conference secretary, Dr. V. V. Gupte, 19 Ph. Mehta Rd., Bombay 1.

Wayne University Postgraduate Course.—The Department of Ophthalmology of Wayne University College of Medicine will give nine months' training in Basic Ophthalmology, beginning Sept. 12, 1955.

Six mornings a week are spent in lectures and laboratories. Each afternoon students are assigned to eye clinics of affiliated hospitals. A fundus clinic is held weekly, as is one on muscles.

Students are given 120 hours of training in physiological optics, 122 hours in histology and pathology, 60 hours in biochemistry, 40 hours in neuroanatomy, etc.

Tuition is $500. Brochures on the Basic Science course will be mailed upon request. For further information, write Dr. A. D. Ruedemann, chairman, Department of Ophthalmology, 690 Mullett St., Detroit 26.

New Calibration Scale for Schiøtz, Gradle-Schiøtz, and McLean Tonometers.—The Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology, at its meeting of Sept. 20, 1954, officially approved and adopted a new calibration scale for Schiøtz, Gradle-Schiøtz, and McLean tonometers. The new scale, referred to hereafter as the 1954 scale, is based on extensive measurements by Friedenwald and Grant. It yields intraocular pressure estimates in approximate agreement with the Schiøtz scale of 1909, somewhat lower than the Schiøtz scale of 1924 and the Committee's scale of 1948. The data on which the new scale is based are published in the Decennial Report of the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology. The Committee believes that the new calibration scale is considerably more accurate than those previously in use.

It is important to realize that the clinical significance of the tonometer scale readings is in no way changed by this new and more correct estimate of what a given scale reading means in millimeters of mercury. For example, the average scale reading on normal eyes with the standard Schiøtz tonometer is generally found to lie between 5 and 6 scale units with the 5.5 gm. load. This is still the average normal reading, but the new calibration scale indicates that this average normal reading corresponds to 15 to 18 mm. Hg, that is, to values considerably lower than was previously thought.

Similarly, a scale reading of 3.0 or less with the 5.5 gm. weight has previously been regarded as suspicious evidence of glaucoma, and this remains true. This concept has previously been expressed in terms of "the upper limit of normal." More precisely, it may be stated that scale readings of 3.0 or less with the 5.5 gm. weight are rarely obtained in normal eyes. The new calibration scale translates this statement to read: "Intraocular pressures higher than 25 mg. Hg on the new scale are rarely encountered in normal eyes."

The chart shown below refers to the standard Schiøtz instrument with concave plunger base. Charts for the Gradle-Schiøtz and the McLean tonometer may be obtained from the respective manufacturers.

The Committee herewith officially recommends the adoption of the 1954 scale.

The 1954 Calibration Scale for Schiøtz Tonometers

Tonometer Reading	Pressure, Mm. Hg			
	Load, Gm.			
	5.5	7.5	10.0	15.0
0.0	39.8	58.4	81.7	126.8
1.0	33.6	49.9	70.6	110.4
2.0	28.4	42.9	61.3	96.7
3.0	24.1	36.9	53.4	84.9
4.0	20.4	31.8	46.5	74.8
5.0	17.3	27.4	40.6	65.9
6.0	14.6	23.5	35.4	58.0
7.0	12.4	20.2	30.8	51.1
8.0	10.4	17.3	26.8	44.8
9.0	8.7	14.7	23.2	39.3
10.0	7.3	12.5	20.0	34.3
11.0	6.1	10.6	17.2	29.8
12.0	5.0	8.9	14.7	25.8
13.0	....	7.5	12.6	22.3
14.0	....	6.2	10.7	19.1
15.0	....	5.2	9.0	16.3
16.0	....	....	7.5	13.8
17.0	....	....	6.3	11.7
18.0	....	....	5.2	9.8
19.0	....	....	....	8.2
20.0	....	....	....	6.8

SOCIETY NEWS

New Jersey Ophthalmological Society.—Dr. Hubert N. Alyea, Professor of Chemistry at Princeton University, addressed the members of the New Jersey Ophthalmological Society and their guests Thursday, Nov. 11. Dr. Alyea spoke on "Atomic Energy: Weapon for Peace."

Dr. C. Byron Blaisdell, chairman of the Board of Trustees of the Medical Society of New Jersey, was a guest of honor at the dinner which preceded the evening program.

The following men were elected for office for the year 1955: Dr. George P. Meyer, of Camden, president; Dr. Lee W. Hughes, Newark, vice-president; Dr. Charles E. Jaeckle, East Orange, secretary, and Dr. Jay E. Mishler, Atlantic City, treasurer.

Dallas Southern Clinical Society.—The Dallas Southern Clinical Society has announced its annual Spring Clinical Conference, to be held March 14 to 17, 1955. Among the honor guests will be Dr. Joel J. Pressman, of Los Angeles, and Dr. G. O. Proud, of Kansas City, representing otolaryngology, and Dr. Paul A. Chandler, of Boston, and Dr. Harold G. Scheie, of Philadelphia, representing ophthalmology.

Dallas Academy of Ophthalmology and Otolaryngology.—The Academy will have as its honor guest, on Feb. 1, 1955, Dr. Michael J. Hogan, of San Francisco. Dr. Hogan will deliver a lecture at 4 p. m. on "Observations on the Pathology and Management of Certain Postcataract Complications." At 7:30 p. m. he will lecture on "Certain Observations on the Diagnosis and Management of Patients with Uveitis."

The meeting of the Academy on Jan. 11 will feature a presentation and discussion of slides demonstrating eye, ear, nose, and throat pathology by Dr. C. T. Ashworth, of Fort Worth, and Dr. Louis S. Smith, of Dallas.

Dr. Morris F. Waldman is president of the Dallas Academy of Ophthalmology and Otolaryngology, and Dr. M. Ray Harrington is its secretary.

Books

Documenta ophthalmologica. Volume VII-VIII. Editors, G. von Bahr, J. ten Doesschate, H. Fisher-von Bünau, J. François, H. Goldman, G. Lo Cascio, H. K. Müller, Jean Nordmann, A. J. Schaeffer, and Arnold Sorsby. Price, 125 guilders. Pp. 758, with 13 plates. Dr. W. Junk, 13, van Stolkweg, The Hague, Netherlands, 1954.

The last two volumes, combined in one, of the *Documenta* contain the following monographs:

Obituary of Prof. J. van der Hoeve, by M. D. Colenbrander.

A Symposium on the Retinal Circulation, held at Strasbourg, June 15 and 16, 1951, at which the following papers were presented:

Ophthalmodynamometry of Baillart: Its Value and Precision.	E. B. Streiff, Lausanne
Retinal Arterial Circulation in Arterial Hypertension	A. Couadau and J. Planques, Toulouse
Evaluation of the Intracranial Circulation by Means of Retinal Arterial Pressure Measurements	E. Weigelin, Bonn
Physiopathology of the Capillary and Venous Circulation of the Retina	A. Fritz, Bruxelles
General Conclusions	P. Bailliart, Paris

Papers presented at a Symposium on Strabismus, which was held on the occasion of the 107th meeting of the Netherlands Ophthalmological Society in December, 1943. The papers presented at this Symposium, together with the discussions, were printed, and copies were distributed to the members of the Society. The remaining copies, which were kept to be distributed to those who might subsequently desire them, were lost during the German occupation. It was decided, therefore, to republish these papers in the present issue of the *Documenta*. They are as follows:

Binocular Vision and Fusion Movements	F. P. Fischer and J. W. Wagenaar
Amblyopia and Squint	J. van der Hoeve (deceased)
Strabismus and Heredity	P. J. Waardenburg
Operative Treatment of Strabismus	H. J. M. Weve
Conservative Treatment of Strabismus	W. P. C. Zeeman
Optokinetic Nystagmus	C. O. Roelofs

In this collection, these papers do not represent the exact presentations at the Symposium. The authors were invited to change their contributions if they so desired, in the light of the discussions and in the light of their experiences over the intervening years. One author, Dr. J. A. van Heuven, had resigned from the Society and taken up his residence abroad. Dr. Fischer and Dr. Wagenaar prepared the chapter on Binocular Vision and Fusion Movements for publication to replace Dr. van Heuven's paper.

The *Documenta* closes with an article on Experimental Keratoplasty, by Yap-Kie-Tiong.

Textbook of Ophthalmology. Volume VII: Summary of Systemic Ophthalmology and General Index. By Sir Stewart Duke-Elder. Price, $7.50. Pp. 244. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1954.

In the volume entitled "Summary of Systemic Ophthalmology," which customarily we call medical and neuro-ophthalmology, Sir Stewart has provided us with a summary of references indicating where each subject can be found in the previously published six volumes. The summary is divided into four main headings: (1) Infective Systemic Diseases, (2) Non-Infective Systemic Diseases, (3) Diseases of the Central Nervous System, and (4) Diseases of the Skin. Each section is broken down into subjects arranged alphabetically; for example, in the section on infective systemic diseases, the first entry is "acrodynia" and the last "zoster." After each entry the page or pages are given where the subject is treated, and the appropriate volume in which the page is to be found can be determined from the key at the top of each page. This system in itself would be quite unworkable were it not for Sir Stewart's genius in coordination. Under each heading a small but adequate script not only covers the points made separately in different volumes, but skilfully weaves the whole into a unified picture. As an example, the entry under "Poliomyelitis" is culled: "(Infantile Paralysis). A relatively common virus disease characterized by respiratory and gastro-intestinal symptoms and typically complicated by involvement of the central nervous system. In these circumstances ocular symptoms are common, including various types of ophthalmoplegia, usually nerve VI, with ptosis, 4101, and pupillary lesions which include anisocoria and hippus, 3748; paralysis of accommodation may occur, 4434. Temporary palsies may be a relatively frequent cause of strabismus. Facial palsy is rare, 5169. Conjugate palsies, 4161, paralysis of divergence, 4176, and convergence, 4172, nystagmus, 4230, and opsoclonia, 4197, may be evident. Occasionally papilloedma and optic neuritis may be associated with meningeal symptoms. *Treatment* is unsatisfactory and symptomatic."

Because the treatment of disease processes in general has changed drastically since the first six volumes were published, a short note indicating modern methods of treatment has been inserted under each heading. There are occasional instances where the subject has not been previously presented, "Infective Mononucleosis," for example. These are covered in the text by adequate documentation without referring to any previous volumes.

Following the summary of systemic ophthalmology is a general index. This considerably enlarges the indices appearing in each volume. A postscript tells us that the final volume, on operative surgery, will not appear, as planned. The reasons Sir Stewart gives are cogent, but nonetheless it will be a disappointment to the ophthalmological world that this single phase of ophthalmology has not been included. Regardless of the fact that there are excellent books on ocular surgery in every language, there is no one other than Sir Stewart who has the skill to bring together the world's literature on each phase of ophthalmology and construct out of it a book peculiarly and patently his own. To offset our disappointment, Sir Stewart promises to turn his energies to revising the first volume, which by now has suffered from the rapid advances of knowledge.

The postscript ends with a paragraph so tyically representative of his free and gracious style of writing that we include it as a fitting finale to this great work: "If, therefore, more writing is to be done, if this book is in some small way to attempt to play the part to which any Textbook worthy of the name should aspire—to integrate the facts of science rather than record them, to be vigilant for knowledge but no less vigilant for the truth of that knowledge, to ease the transition from the groping past to the dissatisfied present and on to the uncertain future, and at the same time to preserve through the transition the essential continuity of all that is good by weaving it into a coherent philosophy—it would seem the better part to return to the first volume and seek to remedy its present shortcomings by adding to it the progress made during the last quarter of a century."

Augensymptome bei Nervenkrankheiten. By Werner Kyrieleis. Price, DM 32. Pp. 153, with 35 illustrations. Walter de Gruyter and Company, Genthinerstrasse 13, Berlin W 35, 1954.

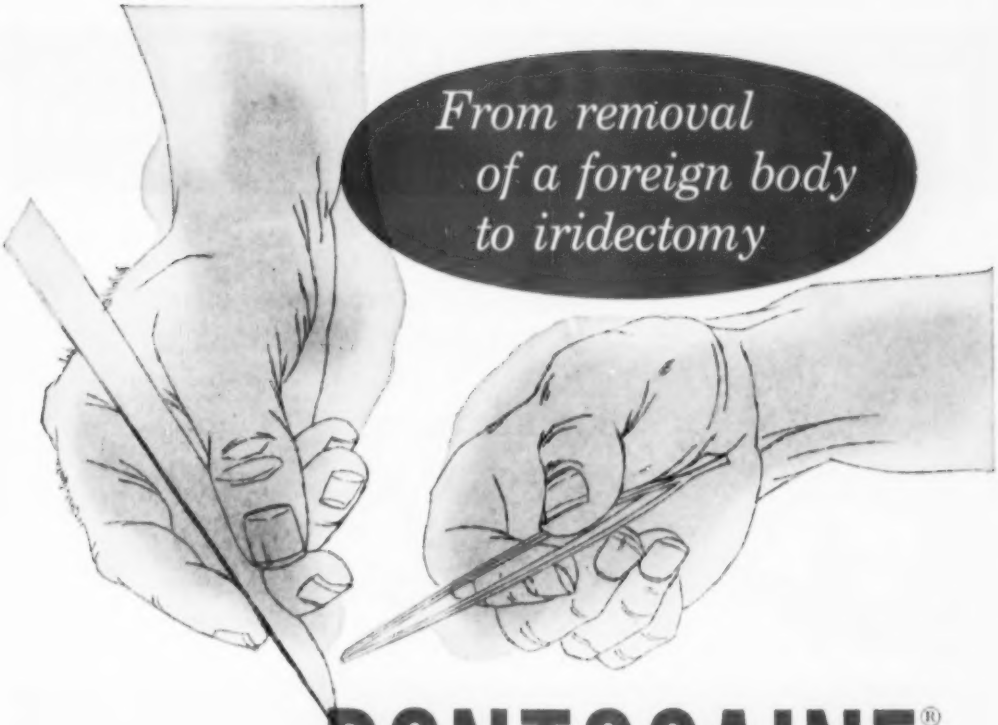
The author believes that many general physicians avoid neuro-ophthalmological problems because they consider them extremely complicated. He wrote this book to simplify neuro-ophthalmology. Insofar as this is possible by presenting a very abbreviated picture, the author has succeeded. This is definitely an introduction to the subject and since it is in German, will hardly be of interest to the average American reader. The book is divided into two parts: the first considering the eye symptoms in nervous diseases, and the second detailing those nervous diseases which have eye symptomatology. The book is well written in simple, straightforward German, and the illustrations are good.

Connective Tissue in Health and Disease. By G. Asboe-Hansen. Price, $7.50. Ejnar Munksgaard, 6 Norregade, Copenhagen, 1954.

Although this book is largely of interest to pathologists, the ocular pathologist will undoubtedly find it useful. There is a small chapter on the mesenchymal aspects of ophthalmology by Eric Godtfredsen.

Human Heredity. By James B. Neil and Silliam J. Schull. Price, $6.00. University of Chicago Press, 5750 Ellis Ave., Chicago 37, 1954.

This book is mainly for the advanced student of biology or the researcher in the field of genetics. There are, however, references to many conditions of interest to ophthalmologists, such as pigmentary degeneration of the retina, retinoblastoma, cataract, and chorioretinal degeneration. There are also references to many diseases in which the eyes are involved. Since the authors' approach is mathematical, the use of the book will be still further limited. The importance of genetics in ophthalmology is growing rapidly, and for those who wish to make a serious study of the subject this book can be recommended.



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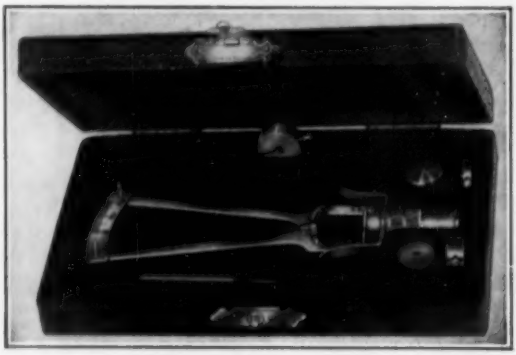

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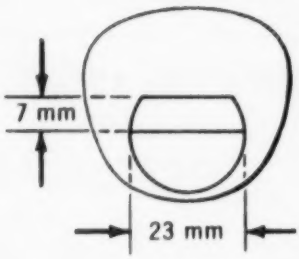

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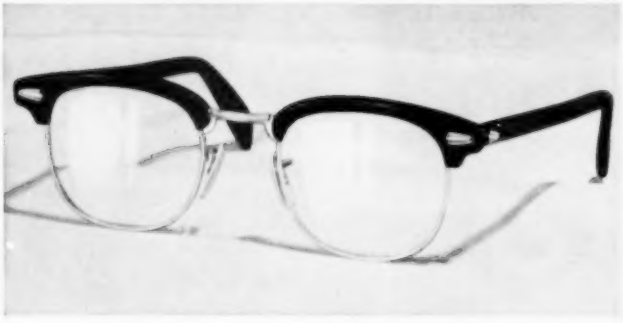

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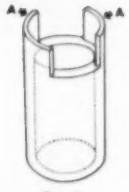

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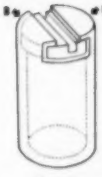

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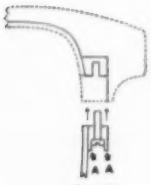

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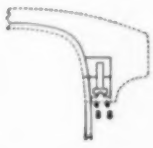

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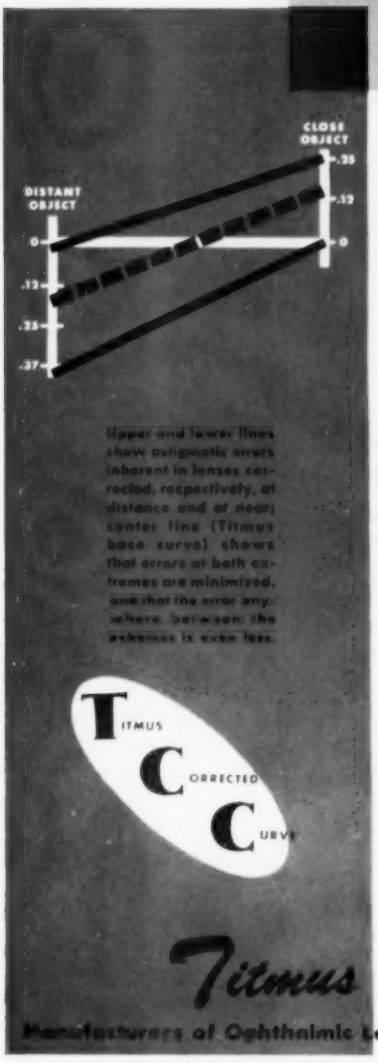
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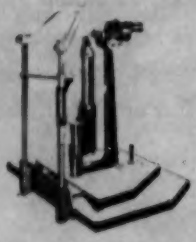

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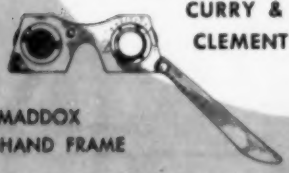

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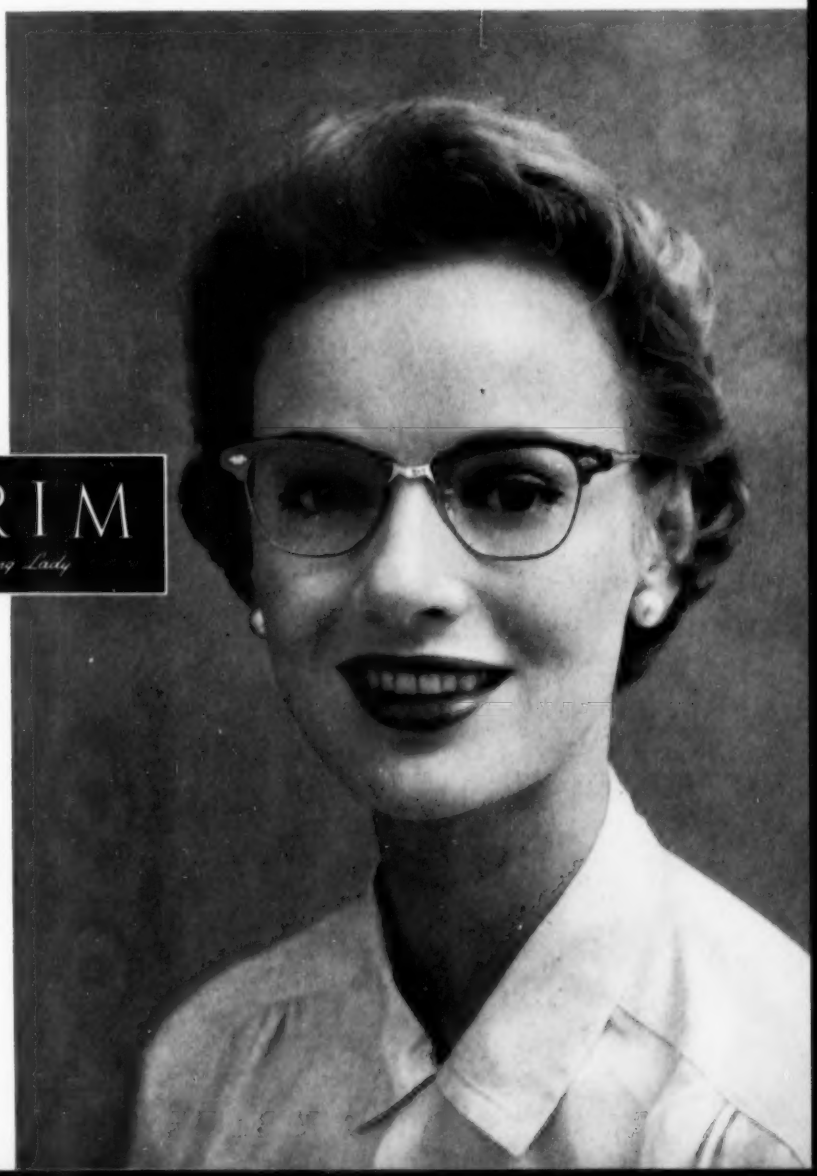

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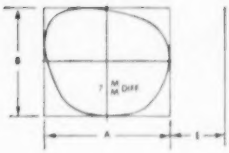

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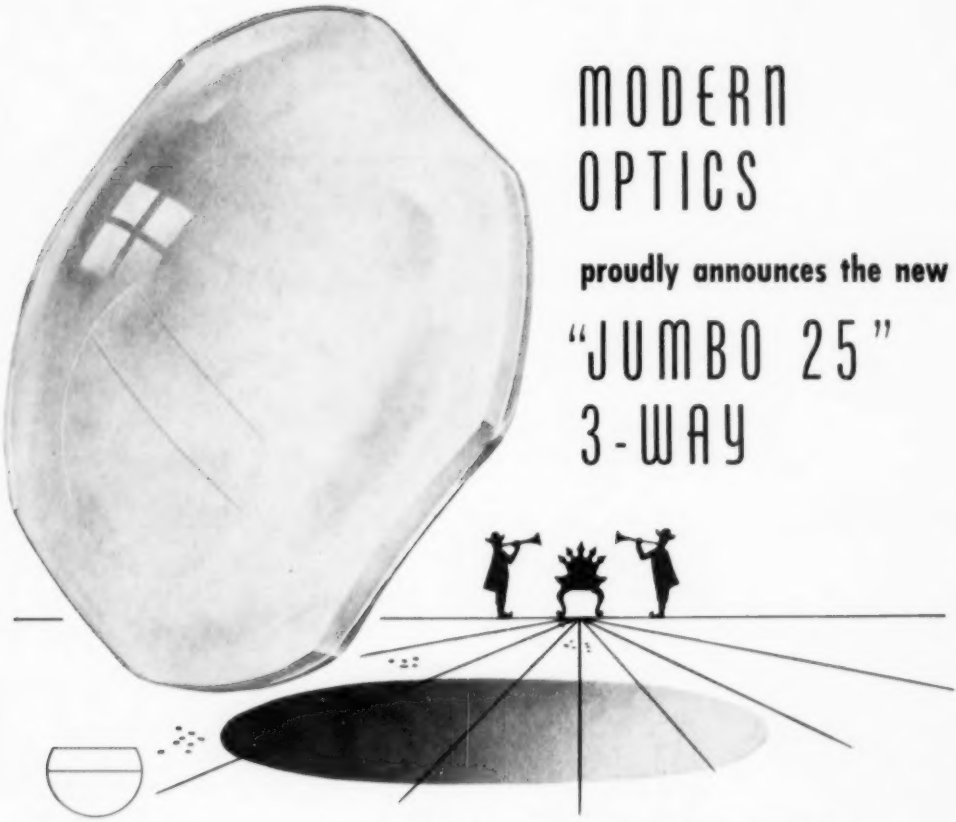

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